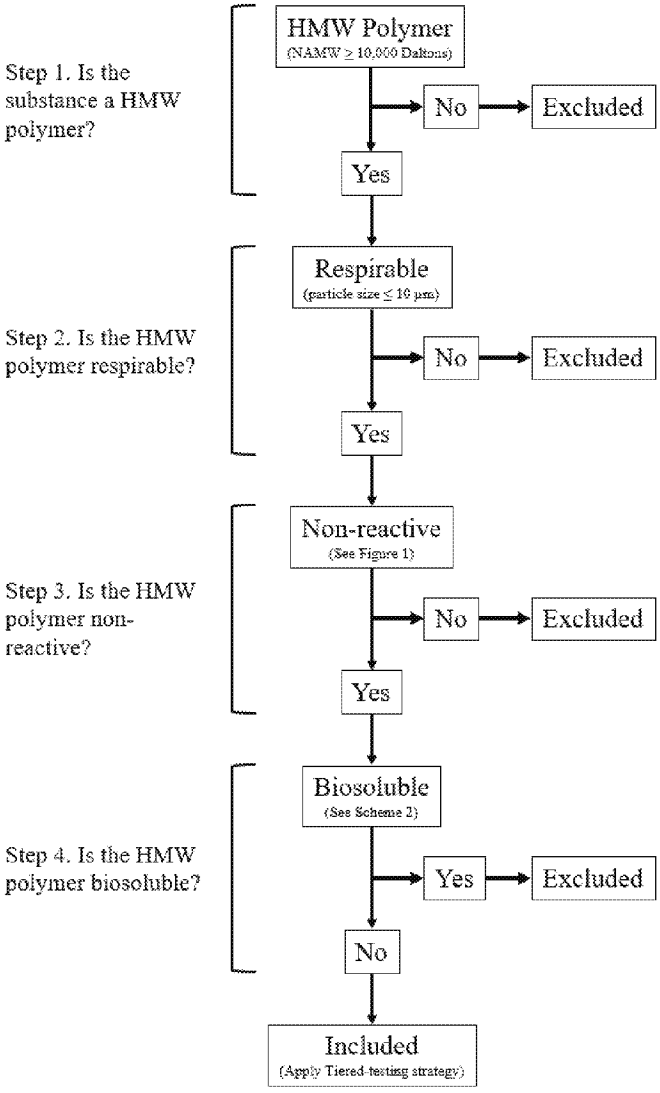
type><contributors><authors><author>Fronius, M.</author><author>Clauss, W.G.</author><author>Althaus, M.</author></authors></contributors><titles><title>Why do we have to move fluid to be able to breath?</title><secondary-title>Frontiers in Physiology</secondary-title></titles><periodical><full-title>Frontiers in Physiology</full-title></periodical><pages>5, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357553/pdf/fphys-03-00146.pdf</pages><volume>3</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The second value is based on the German FIOSH biosolubility cutoff of 1 mg/L for granular biopersistent particles. We propose application of this cutoff as a surrogate for estimating the biosolubility HMW polymers in the lysosomes of alveolar macrophages (*e.g.*, artificial lysosomal fluid).

The above screening criteria for respirability, reactivity, and biosolubility provide a framework for determining inclusion/exclusion from the HMW polymer category, as shown in Scheme 2. The screening criteria may be used for determining whether further evaluation of the new chemical substance is warranted using the tiered-testing strategy discussed later in this document.

Scheme [SEQ Scheme * ARABIC]. Framework for determining whether a chemical substance is included/excluded from the HMW polymer category.



Based on the above information, the HMW polymer category was defined to include a variety of respirable, non-reactive (*i.e.*, low toxicity), and poorly soluble HMW (*i.e.*, ≥ 10,000 Daltons)

materials, which meet the ~~above-stated~~ criteria for these parameters. HMW polymers ~~meeting these criteria are those which~~ are typically formed through various polymerization processes. ~~Chemical substances~~, included ~~are~~ branched and linear polymers, as well as co-polymers produced by random, block, graft, or other techniques. Crosslinked polymers were included in the category because crosslinking can decrease water solubility, but crosslinking was not necessary for inclusion. Therefore, the representative members of this category were refined to include polyacrylates/methacrylates, polyvinyl polymers, polyamides, and polyurethanes/polyureas. The water-dispersible forms polyacrylates/metacrylates and polyurethanes/polyureas would not present hazards for lung overload and are not included in the HMW polymer category [ADDIN EN.CITE ADDIN EN.CITE.DATA]; however, despite their exclusion from the category, they would need to be assessed for other potential hazard concerns. A summary of the structural features of these chemical substances and the chemical boundaries that were established is shown in [REF _Ref46674591 \h * MERGEFORMAT].

[EMBED ChemDraw.Document.6.0]

Figure [SEQ Figure * ARABIC]. Representative members of the HMW polymer category. Structure A, on the left, is representative of polyacrylate/methacylate members, where R is H or methyl; R' and R'' are typically alkyl or substituted alkyl, although there are currently no limits on the substituents. However, charged groups such as carboxyl groups or amine groups would tend to make the polymer dispersible in water rather than insoluble in water. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Acrylamide and methacrylamide monomers (NR'_2 replaces OR' or OR") may also be present. Structure B, on the right, is representative of polyvinyl members, where R is H or C1-C > 20. R' is typically methyl, CN, acetyloxy, Ph or Cl, although there are no current limits on R'. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Copolymers (e.g., including both acrylate/methacrylate and vinyl monomers) are also members of this category. Structure C, on the bottom, is representative of the polyamides group and is made of condensation polymers in which the linkages are all amide functional groups. An example is polycaprolactam, shown.

Hazard Identification

TSCA and its implementing regulations do not require upfront testing on new chemical substances. Therefore, when assessing new chemical substances, EPA generally identifies toxicological analogues to inform the potential hazards for the new chemical substances. The

systematic review of the literature was used to identify inhalation studies that assessed endpoints indicative of "overload" for potential toxicological analogues. For the purpose of defining this chemical category, overload has the same definition as identified by EPA (1996) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>59</RecNum><DisplayText>[37]</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797014">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume II of III</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>774, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=219821</pages><volume>EPA/600/P-95/001bF</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]: "This is defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate which exceeds the capacity of that clearance pathway. It is a nonspecific effect noted in experimental studies, generally in rats, using many different kinds of poorly soluble particles (including TiO_2, volcanic ash, diesel exhaust particles, carbon black, and fly ash) and results in A [alveolar] region clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs and increased translocation of

particles into the interstitium." The relevant studies ~~that were identified~~ are summarized below, followed by the selection of studies on toxicological analogues that may serve as representative points of departure for assessing the potential hazard for overload ~~of some~~for new chemical substances.

Human Data

The hazard concerns discussed ~~herein~~ are limited to chronic effects in the ~~lower respiratory tract~~pulmonary (alveolar) region of rats exposed to HMW polymers. Epidemiological studies have shown increased lung burdens in workers chronically exposed to poorly soluble particles (PSPs), such as former coal miners; however, studies ~~have shown that~~with rodent models overpredict lung burdens in humans if adjustments are not made for kinetic differences in clearance and retention [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This is consistent with findings from well-conducted epidemiological studies, which have not identified an association between occupational exposure to PSPs and an increased cancer risk. Oberdorster (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[38]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-

title></periodical><pages>123-135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>] concluded that "evidence in humans suggest that particle-overloaded lungs, *e.g.*, in coal workers, respond with fibrosis, but no increased incidence in lung tumors has been found in this group". It has also been reported that "epidemiological data from production workers demonstrate no correlation between PSP exposure and lung cancer or other non-malignant respiratory diseases" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Though these investigations focused on PSPs, the available, yet limited data on HMW polymers provide comparable results. For example, in a recent retrospective study of Xerox workers employed between 1960 and 1982, workers exposed to toner did not show an increased risk of "all-cause" or "cause-specific" mortality. The categories evaluated included cancer (*e.g.*, lung), diabetes, cardiovascular disease, and others [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Aside from this one epidemiological study on toner exposures, the ~~available studies that evaluated~~ evaluation ~~potential hazards from~~of exposures to HMW polymers were limited to inhalation studies conducted in experimental animals as summarized below and described in further detail in Section 2 "Experimental Animal Inhalation Studies on HMW Polymers" of the Supplemental Information file.

Animal Data - Noncancer Effects

Inhalation studies performed in rats and hamsters have demonstrated effects ranging from inflammation to fibrosis after inhalation exposure to several HMW polymers including print toners comprised largely of styrene/butylmethacrylate copolymer and polyvinyl chloride dust. Several of these studies were conducted according to validated test guidelines and under good

laboratory practice (GLP) standards, and in some cases published in the peer-reviewed literature. A summary of these studies is provided below.

A series of sub-chronic and chronic studies were performed to test the inhalation effects of a water-insoluble styrene/butylmethacrylate polymer (the primary component of toner used in copy machines) of MW 70,000 in rats. In a subchronic 13-week study, rats were exposed to aerosol concentrations of toner at 0, 1, 4, 16, and 64 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. Dose-related increased lung weight and histological lesions (thickening of alveolar structure due to hypertrophy and hyperplasia of Type II cells) were seen in animals exposed to 16 and 64 mg/m^3. These exposure concentrations also resulted in a dose-related decrease in lung clearance, as measured by the retained quantity of the test substance in excised lungs, and increased lung particle burden [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>]. The NOAEC from this study was 4 mg/m^3.

Bellmann *et al.* (1992) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[42]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug

effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>] performed an additional 13-week study using the same test substance ~~used by~~as Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>] and included an extended 15-month post-exposure monitoring period. Rats were exposed to aerosol concentrations of toner at 0, 10, or 40 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study authors measured retention of the toner in the lungs and lung-associated lymph nodes (LALN) by photometric determination in dissolved tissues; clearance was monitored using tracer particles, and pulmonary effects were identified from enzymatic activities and differential cell counts in bronchoalveolar lavage fluid (BALF). The study authors identified clearance half-lives of 277 and 2,845 days for the low- and high-dose exposure groups, respectively, and reported pulmonary effects, as evidenced by increases in protein and enzyme markers of tissue damage in BALF that were partially reversible at 10 mg/m^3 and not reversible at 40 mg/m^3 [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[42]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health

Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>].

Muhle *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>] and Bellmann *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1991</Year><RecNum>3</RecNum><

DisplayText>[44]</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844572">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Kilpper, R.</author><author>MacKenzie, J. C.</author><author>Morrow, P.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats</title><secondary-title>Fundam Appl Toxicol</secondary-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>300-13</pages><volume>17</volume><number>2</number><edition>1991/08/01</edition><keywords><keyword>Aerosols</keyword><keyword>Animals</keyword><keyword>Body Burden</keyword><keyword>Dust/adverse effects</keyword><keyword>Female</keyword><keyword>Half-Life</keyword><keyword>Lung/*metabolism</keyword><keyword>Lymph Nodes/metabolism</keyword><keyword>Male</keyword><keyword>Pulmonary Alveoli/metabolism</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Sex Factors</keyword><keyword>Silicon Dioxide/*metabolism</keyword><keyword>Titanium/*metabolism</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590 (Linking)</isbn><accession-num>1662649</accession-

num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1662649</url></related-urls></urls><electronic-resource-num>10.1016/0272-0590(91)90220-x</electronic-resource-num></record></Cite></EndNote>] reported findings from a chronic 24-month exposure study in rats exposed to toner at aerosol concentrations of 0, 1, 4, or 16 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study was performed according to OECD No. 453 Combined Chronic Toxicity/Carcinogenicity Studies ~~and~~ under GLP standards. The study authors reported dose-related impaired particle clearance, elevated lung particle burden, and lung effects (fibrosis, BALF markers of tissue damage, and increased lung weight) at 4 and 16 mg/m^3, with a NOAEC of 1 mg/m^3.

Unpublished subchronic (3 months) and chronic (18 months) hamster studies of the same print toner tested by Muhle *et al.* (1990, 1991) and Bellman *et al.* (1991, 1992) [ADDIN EN.CITE ADDIN EN.CITE.DATA] showed similar effects ~~similar~~ to those in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The unpublished 3-month study was hampered by disease and mortality unrelated to treatment. In the unpublished 18-month study, the hamsters were exposed to concentrations of 0, 1.5, 6, or 24 mg/m^3 for the first 5 months and then concentrations of 0, 4, 16, or 64 mg/m^3 for the remaining ~~time~~test period. At all exposure concentrations, the hamsters exhibited macrophage accumulation, interstitial inflammatory cell infiltration, and bronchiolar/alveolar hyperplasia, along with particle deposits and lymphatic hyperplasia in the LALNs. At the mid- and high-exposure concentrations, fibrosis and alveolar PMN infiltration were noted at the end of exposure and/or after the 5 month post-exposure recovery period; the highest exposure group also exhibited increased lung weight and effects on BALF parameters

(increased cell number, macrophage count, LDH, β glucuronidase, total protein, and hydroxyproline). The LOAEC for this study was in the range of 1.5 to 4 mg/m^3.

Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] performed an eight-month inhalation study in rats exposed to an aerosol of PVC powder at 0, 3.3, 8.3, or 20.2 mg/m^3 (MMAD = 1.3 μm; GSD = 2.07; density = 1.3 g/cm^3) for 5 hours/day, 5 days/week. Retention, clearance, and pulmonary effects were evaluated, as reported previously by these same authors. Using radiolabeled (^{85}Sr) polystyrene particles as tracers, these authors showed that pulmonary clearance was significantly decreased in rats after seven months of exposure (25 hours per week)

to PVC powder at concentrations ≥ 3.3 mg/m^3. Mean alveolar clearance half-times increased with exposure from 1.2-fold higher than controls to 3.2-fold higher than controls at concentrations from 3.3 to 20.2 mg/m^3. The study authors calculated half-times for alveolar clearances of 71, 122, and 184 days at exposure concentrations of 3.3, 8.3, and 20.2 mg/m^3, respectively, supporting that lung overload occurred at concentrations ≥ 3.3 mg/m^3 for this water-insoluble polymer.

Animal Data - Cancer

Chronic inhalation exposure data specifically pertaining to HMW polymers are limited to a 24-month rat study of print toner and an 18-month hamster study of print toner [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-

title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>]. No increased in the incidence of tumors ~~incidence~~ was observed in either study; however, interstitial and alveolar lung pathology has been documented in long-term inhalation studies on these polymers. See section on "Animal Data - Noncancer Effects" above.

Supporting Information

An *in vitro* study was identified and reviewed that may be relevant for determining the reactivity/non-reactivity of HMW polymers that do not meet the initial FG and/or FGEW screening criteria.

Wiemann et al. (2016) [ADDIN EN.CITE ADDIN EN.CITE.DATA] developed an *in vitro* assay to test nanoparticles for predicting biologically active ~~toxicity~~ from passive (*i.e.*, overload condition) toxicity. The assay ~~uses~~ used rat NR8383 alveolar macrophages in cell culture

medium incubated with test material ~~in cell culture medium, and~~to assesses toxicity *via* measurement of LDH, glucuronidase, and tumor necrosis factor α (TNFα) (after 16 hours exposure), and hydrogen peroxide (after 1.5 hours) ~~in the cell culture supernatant~~. The authors tested 18 inorganic nanomaterials using the assay, as well as corundum as a negative control and quartz DQ12 as a positive control. The size and shape of the test substances ranged from 9 nm to <30 µm and from 15 m^2/g to 200 m^2/g. Based on data from short term inhalation studies, each test material was categorized as either active (NOAEC <10 mg/m^3 for adverse inflammatory action in a 5-day inhalation study) or passive (*i.e.*, inducing nonspecific cell overload). The *in vitro* assay used a particle surface area-based threshold of <6000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in µg/mL) to determine the biological relevance of the lowest observed significant *in vitro* effects ~~threshold for active toxicity was a surface-area/volume concentration of 6,000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in µg/mL)~~ in at least two of the four measured parameters ~~measured in supernatant~~. The results for the nanomaterials ~~tested~~ showed good ~~correspondence~~ correlation between the *in vitro* and *in vivo* parameters (assay accuracy 95%), suggesting that, the assay could be useful in distinguishing specific ("active") toxicity from nonspecific ("passive" or overload) effects on alveolar macrophages. Although only nanoparticles were tested by these authors, this assay may be useful for screening out HMW polymers for inclusion/exclusion in the category, *e.g.*, those identified as "active" would be inconsistent with the low-concern level and inclusion in the category, whereas those identified as "passive" appear to be consistent with inclusion. Additionally, this assay could be useful for screening polymers with specific toxicities (*i.e.*, excluded from overload category) prior to *in vivo* testing of "overload" for passive polymers.

Quantitative Points of Departure (PODs)

A single epidemiological study of inhaled HMW polymers was identified - the retrospective study of Xerox workers [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This study did not report exposure concentrations associated with the evaluated health outcomes and is therefore not useful for determining quantitative PODs for pulmonary effects of HMW polymers.

A summary of animal studies documenting pulmonary effects after exposure to HMW polymers and the PODs identified from them is provided in [REF _Ref46678612 \h * MERGEFORMAT]. The PODs presented in the table include those from studies meeting the following criteria:

- Exposure was *in vivo via* inhalation (*in vitro*, intratracheal instillation studies were not included);
- Exposure continued for at least 13 weeks; and
- Critical study information was reported, including exposure concentrations, exposure regimen~~frequency~~, and aerodynamic particle size (MMAD ~~and~~, GSD, and density).

Each study was evaluated to determine whether the data were amenable for BMD modeling.

~~For the polyacrylates and methacrylates subcategory, s~~Several subchronic studies, for the polyacrylates and methacrylates subcategory that met the initial POD selection criteria, are included in [REF _Ref46678612 \h * MERGEFORMAT] ~~that met the initial POD selection criteria~~; however, BMD modeling was not performed on these studies because chronic studies

were available and ~~deemed~~ considered more relevant for ~~the~~ hazard assessment with identifying health protective PODs. Two chronic studies met the POD selection criteria: the published 24-month rat study of 9000 type toner and the unpublished 18-month hamster study of the same toner [ADDIN EN.CITE ADDIN EN.CITE.DATA]. BMD modeling was performed ~~for the data in~~on the rat study performed by Muhle *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel

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exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>], ~~as~~because it used a longer exposure duration, was published in a peer-reviewed journal, and did not change exposure concentrations during the study. , ~~whereas, in t~~The hamster study, modified the exposure concentrations ~~were modified~~ after the first five months. ~~Among t~~The endpoints affected at the LOAEC in ~~that~~ the rat study (macrophages, PMN, and lymphocytes in BAL; incidence of pulmonary fibrosis), only the incidence of fibrosis ~~incidence~~ could be modeled, as the BALF parameters were reported without measures of variability (*i.e.*, standard deviation or standard error). The incidences of lung fibrosis (summed across severity categories) were subjected to BMD modeling, as described in Section 3 "Benchmark Dose (BMD) Modeling Outputs" of the Supplemental Information file. The BMCL from the best-fitting model was 2.5 mg/m^3, as shown in [REF _Ref46678612 \h * MERGEFORMAT].

Only a single study was available for the polyvinyl subcategory; however, BMD modeling on the alveolar clearance for the tracer was not possible because of the absence of reported measures of variability ([REF _Ref46678612 \h * MERGEFORMAT]).

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyacrylates and Methacrylates Sub-category							
9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rats, male and female (288/group); 24 months (6 hr/d, 5 d/wk), 2 months recovery	0, 1, 4, or 16	1	4	2.5 (fibrosis)	Significantly decreased macrophages and increased PMN and lymphocytes in BAL; significantly increased incidence of minimal to mild pulmonary fibrosis	[ADDIN EN.CITE ADDIN EN.CITE.DATA]

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
9000 Toner (styrene/butylmet	Syrian Golden Han:AURA Hamster, male and female,	0, 1.5, 6, or 24 (months 1-5); 0,	ND	1.5-4	Not derived; variable	Significantly increased incidences of bronchiolar/alveolar hyperplasia (males); accumulation of particle-laden macrophages in lungs; interstitial	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>30</RecNum><DisplayText>[51]</DisplayText><record><rec-number>30</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849152">30</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Toner A (styrene/butylmethacrylate random	F344/CrlBR rat, female, (58-66/group); 3 months (6 hr/d, 5 d/wk); up to 6	0, 4, 16, or 64	ND	4	Not derived	Significantly increased incidence slight to moderate accumulation of particle-laden macrophages in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>28</RecNum><DisplayText>[45]</DisplayText><record><rec-number>28</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848985">28</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[42]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author>

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Toner B (styrene/ butadiene random copolymer)	F344 rat, female (50 rats/group for main study) up to 6 mo.	0, 1, 4, 16, or 64	4	16	Not derived	Significantly increased incidence very slight to slight focal/multifocal interstitial inflammatory cell infiltration in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>29</RecNum><DisplayText>[52]</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849070">29</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

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Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyvinyls Sub-Category							

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be

Study Selection for establishing sub-category points of departure (PODs)

In rats, the key events in the development of lung tumors ~~in rats~~ in response to inhalation of inorganic PSPs of low toxicity (as outlined by ECETOC 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>], Bevan *et al.*, 2018 [ADDIN EN.CITE ADDIN EN.CITE.DATA], Driscoll and Borm, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Driscoll</Author><Year>2020</Year><RecNum>40</RecNum><DisplayText>[54]</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595775199">40</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Driscoll, K. E.</author><author>Borm, P. J. A.</author></authors></contributors><auth-address>Healthcare Innovation Partners, Princeton, NJ, USA.
Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA.
Nanoconsult BV, Meerssen, The Netherlands.
Dusseldorf University, Dusseldorf, Germany.</auth-address><titles><title>Expert workshop on the hazards and risks of poorly soluble low toxicity particles</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>53-62</pages><volume>32</volume><number>2</number><edition>2020/03/10</edition><keywords><keyword>*pslt</keyword><keyword>*hazard</keyword><keyword>*inhalation</keyword><keyword>*lung cancer</keyword><keyword>*lung particle overload</keyword><keyword>*particles</keyword><keyword>*risk</keyword></keywords><dates><year>2020</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0895-8378</isbn><accession-num>32149535</accession-num><urls></urls><electronic-resource-num>10.1080/08958378.2020.1735581</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]) are: (1) impaired pulmonary clearance, (2) persistent neutrophilic inflammation, (3) increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and (4) proliferation of cells initiated by secondary genotoxicity (from ROS, RNS, and/or inflammation) and tumor formation.

Though the key events for lung overload from HMW polymers have not been thoroughly studied, the available data ~~as reviewed herein~~ suggests that HMW polymers may lead to lung overload in the rat through similar key events. It should be noted that cytotoxicity to macrophages by a poorly soluble HMW polymer or components present in the polymer may negatively impact clearance *via* alveolar macrophages~~, thereby leading to tumor formation in humans~~. However, substances with these properties (*i.e.*, cytotoxicity) would not be included within the boundaries for the HMW polymers category.

Of the studies listed in [REF _Ref46678612 \h * MERGEFORMAT], PODs of 2.5 mg/m^3 and 3.3 mg/m^3 were identified for the polyacrylates/ methacrylates sub-category and the polyvinyls sub-category, respectively. The 24-month study on the 9000 Toner with a $BMCL_{10}$ of 2.5 mg/m^3 for pulmonary fibrosis was selected as a principle study for polyacrylates/methacrylates because it was the longest duration study ~~on this sub-category of materials~~ and was conducted in the most susceptible species for lung overload (*i.e.*, the rat). Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-

title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] was selected as a principle study for identifying a LOAEC of 3.3 mg/m^3 for the polyvinyls sub-category because it was based on decreased alveolar clearance, which is the first key event in the proposed adverse outcome pathway for lung overload from PSPs in the rat [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These study PODs represent potential starting points for evaluating new chemical substances that fit within one of the HMW polymer sub-categories. EPA may determine that either of these PODs is an acceptable toxicological analogue for chemistries that do not fit within the sub-categories but are anticipated to have ~~comparable or greater~~a potential for ~~causing~~ lung overload in the rat than the new chemical substance under evaluation. For example, EPA generally uses the POD of 3.3 mg/m^3 for quantifying the potential risks of HMW polymers, even for chemistries that would not fall within the polyvinyls sub-category, based on the properties of the new chemical substance ~~compared to the PVC powder~~. Notwithstanding this, we recognize that data on a new chemical substance or an alternative analogue would take precedence over using one of these analogues as the default POD, if EPA concludes there are no study limitations on the new chemical substance or alternative analogue that would preclude the use of those data.

Due to the limited data on HMW polymers, available knowledge about inorganic PSPs was used to make inferences about HMW polymers. Compared to systemic effects, lung overload responses to inorganic PSPs show large variations in susceptibility between and among

mammalian species, with the rat being the only species to develop lung tumors [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. This species-specific response has been explained by species differences in the accumulation of insoluble and respirable particles in the lungs, although cytotoxicity is also an issue with some inorganic PSPs (*e.g.*, crystalline silica). ~~For example,~~ hHumans are at least six times more resistant to attaining lung overload conditions than rats for the following reasons: human alveolar macrophages (AMs) are larger (*i.e.*, average volume = 4,990 μm^3) than rat AMs (*i.e.*, average volume = 1,166 μm^3); humans have a greater number of AMs (*i.e.*, average = 7.0×10^9) than rats (*i.e.*, average = 2.6×10^7); and human AMs patrol a smaller surface area (*i.e.*, average = 22,000 μm^2/AM) than

rat AMs (*i.e.*, average = 140,000 μm^2/AM) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further, the site of retention for poorly soluble particles differs between rats and humans. Nikula *et al*. (2001) [ADDIN EN.CITE <EndNote><Cite><Author>Nikula</Author><Year>2001</Year><RecNum>62</RecNum><DisplayText>[56]</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803440">62</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nikula, K. J.</author><author>Vallyathan, V.</author><author>Green, F. H.</author><author>Hahn, F. F.</author></authors></contributors><auth-address>Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87185, USA.</auth-address><titles><title>Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs</title><secondary-title>Environ Health Perspect</secondary-title><alt-title>Environmental health perspectives</alt-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>311-8</pages><volume>109</volume><number>4</number><edition>2001/05/04</edition><keywords><keyword>Adult</keyword><keyword>Air Pollutants/*pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Coal</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Dust</keyword><keyword>Humans</keyword><keyword>*Inhalation Exposure</keyword><keyword>Lung/*chemistry</keyword><keyword>Macrophages, Alveolar</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>*Mining</keyword><keyword>*Occupational

Exposure</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Vehicle Emissions/*analysis</keyword></keywords><dates><year>2001</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765</isbn><accession-num>11335177</accession-num><urls></urls><custom2>PMC1240269</custom2><electronic-resource-num>10.1289/ehp.01109311</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] showed that "the relative amounts of intraluminal and interstitial particle load differ markedly between rats and humans with particles being found predominantly in the interstitium in man and intra-luminarly in rats." In rats, accumulation of particulate matter in the intraluminal space leads to adverse "alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses" [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>].

As noted previously, EPA generally uses the polyvinyls sub-category analogue (*i.e.*, PVC powder) POD of 3.3 mg/m^3 for evaluating new chemical substances that may present a lung overload hazard when the chemical properties are comparable ~~between the new chemical substance and the PVC powder~~. The polyvinyls sub-category POD is then subject to the established EPA dosimetry adjustment. Each of these approaches is discussed below. These dosimetric adjustments may also be applied to the polyacrylates/methacrylates sub-category analogue (9000 Toner), as well as to data on new chemical substances or other potential analogues that fit within the chemical boundaries for this category.

As shown in [REF _Ref519678474 \h * MERGEFORMAT], the RDDRs for the PVC powder ranged from 0.501 in the pulmonary region (PU) ~~up~~ to 2.248 in the tracheobronchial (TB) region. Since the effects occurred in the PU region, the PU (surface area: 0.34 m^2 [rat]; 54 m^2 [human]) RDDR was used for deriving a POD_{HEC}, as follows:

$$POD_{HEC} = POD \times RDDR_{PU}$$

or

$$POD_{HEC} = 3.3 \text{ mg/m}^3 \times 0.5 = 1.65 \text{ mg/m}^3$$

Table [SEQ Table * ARABIC]. Depositional fractions and RDDRs for rats and humans.[a]

SPECIES	Extrathoracic (ET)		Tracheobronchial (TB)		Pulmonary (PU)		Thoracic (TB + PU)		Total Respiratory Tract (RT)	
	Surface Area (cm^2)	Depositional Fraction	Surface Area (cm^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction
Rat	15	0.33	22.5	0.068	0.34	0.061	0.342	0.129	0.344	0.459
Human	200	0.24	3200	0.059	54	0.267	54.32	0.125	54.34	0.566
RDD	0.075	1.373	0.007	1.15	0.006	0.229	0.006	1.028	0.006	0.811
RDDR	0.252		2.248		0.501		0.863		1.763	

[a] Inputted values included: MMAD = 1.30; GSD = 2.07; density = 1.3 g/cm^3.

In comparison, the MPPD model was used to conduct simulations to predict retained mass burden in the PU region of female F344 rats exposed in the Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. The geometry model in the MPPD software for the Sprague-Dawley rat was used, but with the Agency default body weight (BW) of 229 grams for female F-344 rats in a chronic study [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD software internally scales ventilation parameters and respiratory volumes based on BW, so this resulted in tidal volume (V_T) of 1.54, a breathing frequency of 166 bpm, functional residual capacity (FRC) of 3.01 mL, and an upper respiratory tract (URT) volume of 0.34 mL. The 229 g rat PU surface area is predicted to be 1997 cm^2. The particle MMAD, GSD of the particle size distribution, and its density were: 1.3 μm, 2.07, and 1.3 g/cm^3, respectively. The regimen and duration of the nose-only exposure in the Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust

overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study was 5 h/d and 5 d/w for 8 months and was used in the simulation. We note that there were discrepancies in the reported duration of exposure of 7 months versus 8 months in Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. However, the Bellmann *et al.*

(1986) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1986</Year><RecNum>77</RecNum><DisplayText>[57]</DisplayText><record><rec-number>77</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595887108">77</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author></authors></contributors><titles><title>The Effect of a "Nuisance" Dust Inhalation of Lung Clearance</title><secondary-title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference</secondary-title></titles><periodical><full-title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference</full-title></periodical><pages>209-211</pages><dates><year>1986</year></dates><urls></urls></record></Cite></EndNote>] abstract consistently reported an 8-month exposure duration; therefore, a duration of 8-months was used.

Using the above experimental conditions, the predicted retained mass in the PU region of F344 rats, shown in [REF _Ref46766078 \h * MERGEFORMAT], demonstrated the goodness of fit of the MPPD model to the experimental data reported by Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. For example, Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>

<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] reported a retained PU mass of 0.56 mg in rats exposed to 3.3 mg/m^3; the MPPD model predicted a retained PU mass of 0.63 mg at this exposure concentration. Additional simulations were conducted using the same three exposure concentration as Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>], but the key input parameters for MMAD, GSD, and density were varied and bounded. Details on the additional simulations are provided under "Section 4 MPPD Modeling Outputs" of the Supporting Information file. These additional simulations reinforce that prediction of overload kinetics is specific to the particle physicochemical properties (size, distribution, and density) and experimental regimen. Such

simulation demonstrations can be useful to defining whether a given particle and exposure conditions achieve overload.

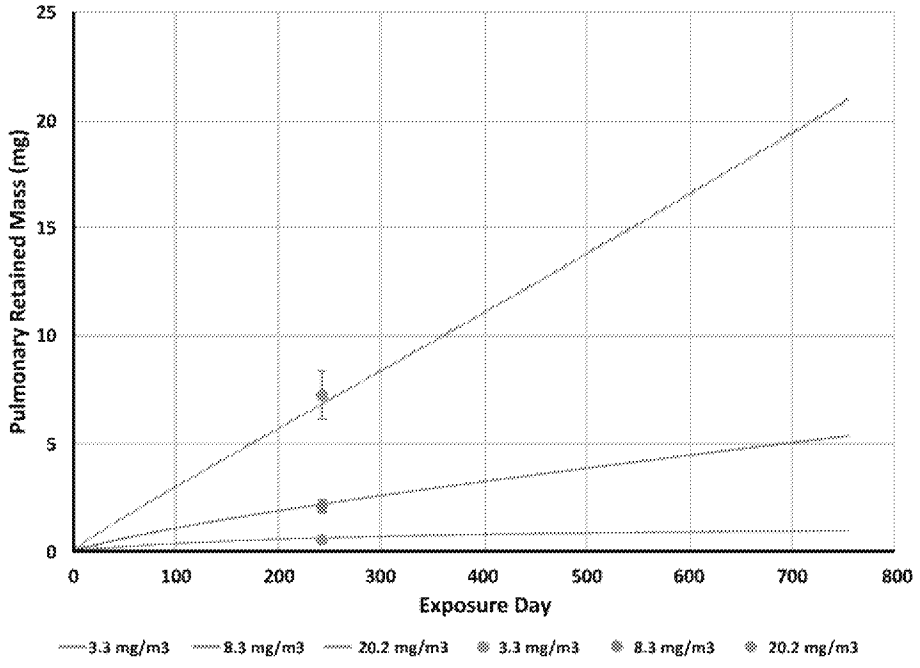

Figure [SEQ Figure * ARABIC]. MPPD predictions for retained PU mass in F344 rats under the exposure conditions for the Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar,

M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. Simulations were performed to characterize the 8-month study with a particle MMAD size of 1.3 μm, a GSD of 2.07, and a density of 1.3 g/cm^3 for three concentrations (3.3, 8.3, and 20.2 mg/m^3). Experimental data for PU burdens are shown as solid circles with standard deviation and the predictions as solid lines for different concentrations.

For extrapolation of the predicted rat retained PU mass to an HEC, human simulations were conducted for adult males with a V_T of 0.992 L and a breathing frequency of 21 bpm, or with 1.364 L and 33 bpm. These ventilatory values are from the ICRP (1994) [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann

ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and represent ventilation associated with activity levels of either light exercise or heavy exercise for adult males. It should be noted that this combination of V_T and bpm for the light exercise ventilation input parameters are equivalent to the default minute ventilation value (V_E) found in [REF _Ref46666189 \h * MERGEFORMAT] of 1.25 m^3/hr. An occupational exposure duration of 40 years was simulated for the human predictions of retained mass in the PU region.

The dose metric used to operationally derive the HEC is the PU retained mass (mg) normalized to the PU surface area (SA) in cm^2 according to the established US EPA methods [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD model estimates a human pulmonary surface area of 66.3 m^2 for an 80 kg adult male. As shown in [REF _Ref46767442 \h * MERGEFORMAT], simulations were performed iteratively to arrive at an HEC that achieved the same internal dose metric (PU mass / PU SA) in humans as was achieved in rats under the experimental conditions reported by Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. As was shown in [REF _Ref46766078 \h * MERGEFORMAT], the predicted retained mass in the PU region corresponds well with the observed experimental data. The last two rows of [REF _Ref46767442 \h * MERGEFORMAT] demonstrate the difference in HEC value due to variation in ventilatory parameters associated with either light or heavy activity.

Table [SEQ Table * ARABIC]. MPPD predictions and HEC calculations for Muhle *et al*. (1990) study of F344 rats exposed to PVC with a particle MMAD of 1.3 μm, GSD of 2.07 and density of 1.3 gm / cm^3.

Exposure Concentration (mg/m^3)	**3.3**	**8.3**	**20.2**
Experimental Rat Retained PU Mass (mg)	0.56±0.16	2.09±0.29	7.24±1.10
Predicted Rat Retained PU Mass (mg)	0.63	2.21	6.88
Predicted Rat Retained PU Mass / PU SA (mg/m^2)	2.8	10.5	36.3
Light Activity 40-Year HEC (mg/m^3)	0.33	1.23	4.25

Heavy Activity 40-Year HEC (mg/m^3)	0.14	0.53	1.84

HEC = human equivalent concentration that results in the same inhaled dose metric (retained PU mass / PU SA) as predicted for the rat. The human ventilatory parameters of the light and heavy activity levels for simulation of 40-year occupational scenario are described in the text.

Category benchmark margin of exposure (MOE)

EPA currently applies a benchmark MOE ~~composite UF~~ of 1,000 ~~as the benchmark MOE for~~to the PVC powder POD of 3.3 mg/m^3. The composite UF consists of default values of 10 for UF_H, UF_A, and UF_L. This default approach was initially established as a conservative means of evaluating new chemistries on HMW polymers, which were anticipated to present a hazard concern for lung overload. ~~However, s~~Several refinements to these values may be made~~, including reducing~~ the The TK and TD components of the UF_A value and reducing the UF_L. Dosimetric adjustments using the RDDR model or the MPPD model, as discussed above, may be applied to calculate a POD_{HEC}, thereby reducing the TK component of the UF_A to 1. Since lung overload is a chronic effect that is manifested primarily based on the retained dose in the PU region, the RDDR model is not necessarily the most appropriate for deriving a POD_{HEC}, given that deposition is a more relevant metric for short-term effects/exposures. However, the RDDR model was used to provide comparative estimates of the MOE to the ~~other approaches versus the~~ respective benchmark MOE, given that the RDDR ~~approach~~ model is recommended in EPA guidance as the default for quantifying POD_{HEC}s for particles. For the TD component, a reduced value of 1 may be applied based on the proposal from the ILSI Workshop Consensus Report on rat lung response to particle overload, which stated: "For both neoplastic and fibrogenic endpoints in the rat, associated with PSP exposures, the work group proposed that the TD component of the interspecies UF be reduced from a factor of 3 to 1, given that chronic active

inflammation in the rat appears to be a more sensitive response than in other species, including humans" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The UF_L may be reduced from 10 to 1 for the PVC powder analogue POD because default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathway~~this dose represented the point at which retardation of alveolar clearance started, based on the retained mass of about 0.5 mg/lung~~. This approach is consistent with EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>], which states that the UF_L "may be altered, depending on the magnitude and nature of the response at the LOAEL". ~~Further, the default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathway~~. Based on the foregoing considerations, the following values are proposed for deriving the benchmark MOE for HMW

polymers, which are generally applicable regardless of whether the POD is derived from an analogue or a new chemical substance.

UF_H = 10: The default value of 10 should be applied, unless there are human data showing which age groups or time periods are the most sensitive to lung overload. This approach is consistent with EPA's guidance for reducing the default UF_H [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>].

UF_A = 3 or 1: A reduced value of 1 should be applied for the TD component based on the ~~proposal~~ consideration documented by Olin (2000). In addition, if the data are amenable for deriving a POD_{HEC}, the dosimetric adjustment for the TK component further supports reducing

this UF [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><Dis
playText>[14, 18]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key
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title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC
20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S.
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https://www.epa.gov/sites/production/files/2014-12/documents/rfd-
final.pdf</pages><volume>EPA/630/P-
02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><
Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-
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Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental
Protection Agency, Research Triangle Park, North Carolina</secondary-
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Protection Agency, Research Triangle Park, North Carolina</full-

title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

UF_L = 10 or 1: A value of 1 should be applied when the POD is based on a study NOAEC or when BMD modeling is applied to derive a BMCL, per EPA guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The default value of 10 should be applied when the POD is based on a study LOAEC; however, a reduced value may be used, when ~~for example,~~ the LOAEC is based on key event 1 from the proposed adverse outcome pathway for PSPs. Reductions in the UF_L based on other key

events should be made on a case-by-case basis and supported by discussion of the key event within the context of an established AOP.

The default and dosimetrically adjusted PODs and benchmark MOEs derived on new chemical substance risk assessments are used to inform risk management options for addressing potential risks. Therefore, values derived using dosimetric adjustments may allow for refined estimates ~~For example, the default POD of 3.3 mg/m^3 and benchmark MOE of 1,000 result in an MOE of 2.0E-01 that would require~~for determining the appropriate engineering controls and/or ~~a respirator with an applied protection factor (APF) of 1,000~~personal protective equipment. ~~In comparison, when dosimetric adjustments are applied using the MPPD modeling outputs, the POD$_{\text{HEC-light activity}}$ of 0.33 mg/m^3 and refined benchmark MOE of 10 result in an MOE 1.7, which indicates that engineering controls and/or a respirator with an APF of 10 would be required.~~

Uncertainties and Limitations

The available toxicological studies for HMW polymers lack data on materials with molecular weights < 70,000 Daltons [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>63</RecNum><DisplayText>[59]</DisplayText><record><rec-number>63</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803909">63</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>High Molecular Weight Polymers in the New Chemicals Program</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/high-molecular-weight-polymers-new</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. In addition, the following uncertainties and study limitations were noted, that if known, may serve to refine the boundaries for this category:

- Physicochemical properties can influence deposition of inhaled particles (*e.g.*, particle size, distribution, density, and hygroscopicity) while ~~and biopersistence and bioreactivity (*e.g.*,~~ solubility, surface chemistry, and composition~~).~~ determine biopersistence and bioreactivity and thereby impact clearance and retention. However, the available studies of test materials in this category are generally missing information on these properties, with the exception of particle size.
- Information on molecular weight was not reported for test materials used in the studies of the PVC powder [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle,

H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>].

- The test materials administered in the 9000 toner studies [ADDIN EN.CITE ADDIN EN.CITE.DATA] included colorant materials (predominantly carbon black) at up to 10%, and the influence of these colorants on the observed effects is unknown.
- The PODs summarized in [REF _Ref46678612 \h * MERGEFORMAT] for the HMW polymers were reported on a mass/volume basis. However, there is evidence that number of particles, particle volume, and/or volume of particles retained in the lung can influence the threshold at which lung overload conditions occur [ADDIN EN.CITE ADDIN EN.CITE.DATA]. ~~Thus, particle density may be an important consideration in identifying a POD; however, the appropriate density metric and how density should be incorporated remain uncertain.~~ Data emerging on nanomaterials and ambient ultrafine particles also increasingly suggest surface area may determine toxicity. Thus, different internal dose metrics should be explored. This can be done readily with dosimetry models as described.

- Particle morphology, reactive groups, and cytotoxicity can impede clearance pathways and induce other mechanisms of toxicity in rodents and humans. These factors include covalent binding to lung tissues, toxicity to clearance macrophages/cilia and particles lodging in pulmonary tissues which may not be considered in aerodynamic models. An *in vitro* macrophage clearance assay utilizing human or primate cells and rat cells would be potentially useful information to determine whether new chemistries fall within or outside the boundaries for this category.

An additional, important consideration pertains to the uncertainty ~~associated~~ association ~~with~~ of the human relevance of lung tumors observed in rats exposed to PSPs. ~~The available data clearly demonstrate that the rat is a sensitive model for non-neoplastic pulmonary effects following repeated exposure to PSPs, which have also been shown to occur in occupational cohorts (*e.g.*, coal miners).~~ The rat ~~also~~ appears to be unique among species with regard to carcinogenesis in the lung due to particle overload. Lung tumors following chronic exposure to PSPs have been reported in rats, but have not been reported in mice, hamster, non-human primates, or humans [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-

Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. Despite the uncertainty in the carcinogenicity of inhaled PSPs, the rat model remains a useful model for lung overload because it is a sensitive model for inflammatory response to PSPs, and ~~because~~ protecting against inflammation and proliferation may also protect against tumor formation [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Tiered-testing Strategy

The POD and benchmark MOE derived herein provide an analogue/read-across approach for assessing new chemical substances that fit within the chemical category boundaries for HMW polymers~~, also defined herein~~. As with any analogue read-across, assessors must carefully consider the comparability of the new chemical substance to the analogue or another acceptable toxicological analogue.; ~~this~~ This framework provides specific criteria for evaluating whether a new chemical substance "fits" into the HMW polymer category (*i.e.*, not chemically reactive, insoluble in water, not expected to be directly cytotoxic, not expected to release toxic degradates). Additionally, we demonstrate the utility of dosimetry modeling to inform evaluation or experimental design.

~~When~~ If information is not available to evaluate whether the new chemical substance fits within the category boundaries and ~~the analogue is appropriate for~~no acceptable toxicological analogue is available for use in a risk assessment, testing should be performed to aid with refining the evaluation of new chemistries that ~~are anticipated to~~may present a potential lung overload hazard. A tiered-testing strategy that is consistent with the reduced vertebrate testing requirements under the amended TSCA is provided. Though this strategy does not completely exclude vertebrate testing, it maximizes the use of NAMs for determining whether vertebrate testing should be considered. This strategy incorporates *in chemico* and/or *in vitro* characterization of the chemical substance in Tier I (*e.g.*, particle size distribution, density, reactivity, and biosolubility measurements). For substances that have particles in the respirable range, are non-reactive, and are not biosoluble, computational screening is included under Tier II to determine whether the HMW polymer is estimated to exceed the clearance t½ in the rat or demonstrate overload under anticipated use conditions. If the HMW polymer is expected to exceed the clearance t½ in the rat, then risk management options or strategic *in vivo* testing is proposed as a final option under Tier III.

Commented [ST6]: Comment from Ann: "Can we add a statement that if the PMN submitter prefers not to use the EPA "analog", they may generate the data on their specific HMW polymer?"

TS: Does the correction to the text make this clear? Can't believe I overlooked that typo so many times.

Commented [ST7]: Comment from Stephanie: "There is no density characterization in Tier I. Do we want to mention it here?"

TS: If this is not a routine measure for HMW polymers, we should add it to the testing since it will be needed to do the model simulations.

Tier I

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- **Particle Size Distribution** or Aerosolized Droplet Size of particle in use (*i.e.*, cascade impactor, laser methods, *e.g.*, OECD TG 110 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>64</RecNum><DisplayText>[61]</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-

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ilibrary.org/environment/test-no-110-particle-size-distribution-fibre-length-and-diameter-
distributions_9789264069688-
en</pages><volume>110</volume><dates><year>1981</year></dates><urls></urls></r
ecord></Cite></EndNote>], OPPTS 830.7520 [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>65</RecNu
m><DisplayText>[62]</DisplayText><record><rec-number>65</rec-number><foreign-
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<title>Particle Size, Fiber Length, and Diameter Distribution</title><secondary-
title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency,
1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-
title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S.
Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</full-title></periodical><pages>13, https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-830-product-properties-test-guidelines</pages><volume>EPA 712-C-96-037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]) of the new chemical substance during specific use(s) (*i.e.*, depending on the intended or known uses of the chemical substances, particle size distribution may need to be tested under more than one use scenario)

- If the % of respirable particles (*i.e.*, ≤ 10 μm) is less than 1 wt% under the conditions of use, or following transport, stop at Tier I.
- If the % of respirable particles (*i.e.*, ≤ 10 μm) is greater than 1 wt% under the conditions of use, or if respirable particles are anticipated or shown to be generated following transport (> 1%), then proceed with reactivity testing, if needed, or biosolubility testing.

- **Reactivity**

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  - If the HMW polymer is a potential concern for reactivity, based on ~~function or~~ other information (*e.g.*, does not meet the E1 FG/FGEW criteria), reactivity should be assessed using an *in vitro* method, preferably discussed with EPA in a pre-notice consultation meeting and prior to study initiation. The assay developed by Wiemann *et al.* (2013) [ADDIN EN.CITE ADDIN EN.CITE.DATA] provides a potential option; however, there are caveats with its use, such as not being validated and uncertainty with whether the test method could be used with HMW polymers, underscoring the recommendation to consult with EPA prior to testing using this method or other test methods.

- If substance is "reactive" (*e.g.*, does not met the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, it would be excluded from the HMW polymer category. If evidence indicates the substance is "non-reactive" (*e.g.*, it does meet the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, then proceed to biosolubility testing.

- **Biosolubility Testing**

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  - Solubility in Gamble's solution (*e.g.*, ECETOC, 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of

Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]), simulated epithelial lung fluid (SELF) (*e.g.*, Boisa *et al.* 2014 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and/or phagolysosomal simulant fluid (*e.g.*, BAUA, 2017 [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[33]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>])

- Employ a simple exponential decay model to predict the dissolution half-life: $P(t)=P0e^{-rt}$, where: P(t) = the amount of some quantity at time t; P0 = initial amount at time t = 0; r = the decay rate; t = time

The exponential decay function is the solution to the first order reaction equation, assuming a constant decay rate, r:

$$\frac{dP(t)}{dt} = -rP(t), P(0) = P_0$$

First order kinetics are used as the basis for lung clearance rates including dissolution and absorption into blood [ADDIN EN.CITE ADDIN EN.CITE.DATA].

- If the solubility data indicate a dissolution rate (*i.e.*, 100 mg/L/day or 72 mg/day) higher than the daily occupational exposure estimate (*e.g.*, default PDR of 50 mg/day), then stop at Tier I.
- If the solubility data indicate a dissolution rate lower than the daily occupational exposure estimate, then proceed with Tier II testing.

If the % of respirable particles is > 1 wt%, the HMW polymer is non-reactive, and the HMW polymer has a dissolution rate that is lower than the estimated daily occupational exposure estimate, proceed to Tier II.

Tier II

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- Perform computational modeling (*e.g.*, MPPD) ~~including the effect of dissolution~~ to predict deposition, clearance, and lung burden for a simulated chronic rat exposure (See, *e.g.*, Ladics *et al.*, 2020 [ADDIN EN.CITE

<EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[23]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]). If dissolution data are not available, assume the test substance is poorly soluble.

- If the ~~clearance t½ is less than 60 days~~MPPD simulations do not indicate overload under the conditions of use, stop at Tier II.

If the ~~clearance t½ is greater than that for PSPs in the rat (*i.e.*, 60 days)~~ simulations indicate overload under the conditions of use, consider risk management options (*e.g.*, engineering controls and personal protective equipment) or proceed to Tier III.

Tier III

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- Strategic *in vivo* testing should be considered, albeit on a case-by-case basis, and after discussions with EPA at a pre-notice consultation meeting. When performed, the testing should include:
    - MPPD simulations to predict for the specific particle size, distribution, and density of the new chemical substance to identify exposure levels where overload is likely to occur.
    - Exposure at concentrations that allow for a concentration-response for low exposures, where pulmonary clearance is not impaired, and a high ~~enough to~~exposure that demonstrates impaired pulmonary clearance of particles and lead to an "overload" condition. It has been shown that in rats impaired clearance starts when phagocytized particle volume exceeds 6% of normal alveolar macrophage volume and clearance stops altogether when phagocytized volume reaches 60% of normal macrophage volume (See, *e.g.*, Borm *et al*., 2015 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and
    - Special attention to pulmonary function tests; blood oxygen (pO_2); lung burden measurements and lung clearance kinetics; collection of BALF for assessment of marker enzyme activities, total protein content, and cell counts; lung retention and clearance; lung weight; and lung histopathology (inflammation and cell proliferation). It is not necessary to evaluate internal organs. OECD TG 413 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>71</RecNum><DisplayText>[66]</DisplayText><record><rec-number>71</rec-

number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838832">71</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>90-Day (Subchronic) Inhalation Toxicity Study</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>23, https://www.oecd-ilibrary.org/environment/test-no-413-subchronic-inhalation-toxicity-90-day-study_9789264070806-en</pages><volume>413</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] and OECD GD 39 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>72</RecNum><DisplayText>[67]</DisplayText><record><rec-number>72</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839002">72</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Guidance Document on Inhalation Toxicity Studies, Series on Testing and Assessment (Second Edition)</title><secondary-title>Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on

Chemicals, Pesticides and Biotechnology</secondary-title></titles><periodical><full-title>Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology</full-title></periodical><pages>106, https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)28/rev1&doclanguage=en</pages><volume>ENV/JM/MONO(2009)28/REV1</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] should be consulted, given that the 90-day subchronic inhalation toxicity study in rats (OECD 413) with a 60-day recovery period is sufficient for identifying lung overload for PSPs in this species [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200

Commented [ST8]: Comment from Anne: "There are also data to support using a 5 day exposure followed by a 28 day recovery may be sufficient to evaluate lung overload in PSP?"

TS: See included text. I modified this slightly from Ann's proposal.

Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

The utility of studies of ~~Research is ongoing to evaluate if studies utilizing~~ shorter exposure duration (*e.g.*, 5 days) followed by recovery is still being investigated~~may bearc useful~~; therefore, ~~if~~ submitters ~~are interested in evaluating the utility of a shorter duration study, such studies~~ should ~~be discussed~~ discuss the applicability of such studies with EPA prior to ~~study~~ initiation.

CONCLUSIONS

In summary, the available toxicological studies on HMW polymers support that the key parameters for determining whether a HMW polymer may present a hazard based on lung overload include: respirability, reactivity, and solubility. These are the same key parameters for lung overload caused by poorly soluble particles (PSP), an extensively studied and ~~well known~~well-known phenomena. ~~-~~The tiered strategy~~approaches~~ proposed in this ~~paper~~article takes advantage of these key factors and evaluates ~~identified for lung overload and apply, as~~their applicableility to HMW polymers. ~~—~~Two HMW polymers were ~~-~~identified as toxicological analogues ~~were identified~~ that may be used for "read across" when evaluating the potential of a ~~to~~ new chemical substance ~~for evaluating~~to result in lung overload. When applicable, the PODs on these analogues may be refined using dosimetry modeling such as simulations with the MPPD model to predict ~~when~~the exposure levels when overload might occur in the experimental species~~The MPPD software provides for a straightforward approach to predict when overload~~

~~might occur in the experimental species~~, to perform interspecies extrapolation to HEC estimates, and to inform inferences for human health risk ~~evaluation~~assessment. For new chemical substances that are not suitable for read across from these toxicological analogues, or when a company prefers to provide data for its specific HMW polymer new chemical substance, the tiered-testing strategy described above provides a framework that minimizes the use of vertebrate animals, and takes advantage of new alternative ~~method~~assays to characterize ~~and~~ key events in a putative AOP for ~~from~~ PSP induced lung overload; ~~with~~while providing information which may be used to determine if there is a potential for ~~informing whether~~for new HMW polymers to present a hazard for lung overload under its condition(s) of use. ~~Concentrations at which overload was not achieved in the rat are relevant to human assessment, as are other endpoints other than tumors at overload.~~ Collectively, the read across approach, ~~Simulations~~ the MPPD model simulations, and the tiered-testing strategy represent a novel approach method that will aid with evaluating new chemical substances to ensure that they do not present an unreasonable risk to human health and advancing the understanding of inhaled particle toxicity~~would also be most useful to design of experiments before costly investments in inhalation studies are made~~. ~~-~~Using these approaches, data on the respirability, reactivity and solubility of HMW polymers will be evaluated by EPA and only when needed, on a case by case basis, will animal studies be considered and discussed with the new chemical substance manufacture. ~~and may also help to~~resulting in a reduction and ~~refiment~~refinement of ~~reduce and refine~~ the number of animals used. ~~-~~The tiered testing approach was developed based on the best available science currently available. ~~-~~It is expected that as new data ~~will be~~is provided to EPA through new substance notifications, ~~and will be evaluated as appropriate to determine if~~ the tiered testing framework

~~requires modification~~will be evaluated and updated as appropriate. ~~-~~This is in line with EPA's Strategic Plan to Promote the Development and Implementation of Alternative Test Methods.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information file contains the following:

Section 1. Systematic Literature Review

Section 2. Experimental Animal Inhalation Studies on HMW Polymers

Section 3. Benchmark Dose (BMD) Modeling Outputs

Section 4: MPPD Modeling Outputs

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ~~‡These authors contributed equally. (match statement to author names with a symbol)~~

Funding Sources

EPA sponsored the initial literature review through a government contract to SRC (68HERH19F0197 (TO#07))~~[insert number]~~. The American Chemistry Council's TSCA Section 5 Testing Consortium sponsored an updated literature review by an independent third party.~~ACC sponsored the supplemental literature review conducted by an independent third party.~~

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Notes

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~~**ACKNOWLEDGMENT**~~

~~Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).~~

REFERENCES

[ADDIN EN.REFLIST]

Message

From: Stedeford, Todd [Stedeford.Todd@epa.gov]
Sent: 7/30/2020 11:07:17 PM
To: Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Ladics, Greg [gregory.s.ladics@dupont.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Snyder, Stephanie [stephanie.snyder@covestro.com]; Tveit, Ann [Ann.Tveit@basf.com]; Irwin, William [Irwin.William@epa.gov]; Salazar, Keith [Salazar.Keith@epa.gov]; Henry, Tala [Henry.Tala@epa.gov]
Subject: revised draft for polymer lung overload + supporting information file
Attachments: Draft manscript insoluble polymers and lung overload - 30 July 2020.ver.1.docx; Supporting Information File - 30 July 2020.ver.1.docx

Importance: High

All,

Please find the attached, revised draft of the lung overload manuscript and the supporting information file for our call tomorrow. I kept all changes in track changes, so you can see the updates based on edits/comments received to date.

Thanks,

Todd

Polymer Lung Overload Category: The Application of a New Approach ~~Methodologies~~ Methodology (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

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KEYWORDS: Inhalation, Lung Overload, New Approach Methods, Particle Toxicity, Risk Assessment~~, (Word Style "BG_Keywords"). If you are submitting your paper to a journal that requires keywords, provide significant keywords to aid the reader in literature retrieval~~.

ABSTRACT

Poorly soluble and non-reactive high-molecular weight (HMW) polymers (≥10,000 Daltons) represent a generic category of substances that are extensively used in industrial and consumer applications (*e.g.*, plastics). Under the 2016 amended Toxic Substances Control Act (TSCA), HMW polymers may qualify for an exemption from the pre-notification requirements that exist for polymeric, new chemical substances. However, for HMW polymers that do not meet the exemption criteria and are produced in a respirable form (*e.g.*, powders), the U.S. Environmental Protection Agency (EPA) will evaluate hazards and risks of these substances for lung overload. In the present evaluation, a systematic review of the literature was performed to identify studies that would aid with defining key properties for determining whether respirable HMW polymers may present an unreasonable risk to human health. These properties included: respirability,

reactivity, and solubility and were used for defining the inclusion/exclusion criteria for a chemical category on HMW polymers. Available inhalation toxicity studies for HMW polymers were evaluated and dosimetric adjustments used to derive human equivalent concentrations for ~~several~~ a toxicological analogues that ~~can~~ may be used as a first step in risk assessments on these substances. Finally, a tiered-testing strategy was developed as a new approach method that maximizes the use of non-vertebrate testing ~~(i.e., NAMs) was developed~~ that may be used to evaluate newer chemistries to determine whether they fit within the chemical category of HMW polymers that may present a lung overload hazard or for refining risk estimates for such chemical substances.

INTRODUCTION

The Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed into law on June 22nd, 2016, thereby amending the Toxic Substances Control Act (TSCA), the nation's primary chemicals management law for regulating new and existing chemical substances. The amendments to TSCA placed new requirements on the U.S. Environmental Protection Agency (hereinafter "EPA" or the "Agency") to reduce and replace vertebrate animals in testing of chemical substances, to the extent practicable and scientifically justified, and requires EPA to make one of the following five determinations for new chemical substances, based on unreasonable risk, sufficiency of information, and exposure:

1. The new chemical substance or significant new use presents an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(A));

2. The available information is insufficient to allow the Agency to make a reasoned evaluation of the health and environmental effects associated with the new chemical substance or significant new use (TSCA §5(a)(3)(B)(i));
3. In the absence of sufficient information, the new chemical substance or significant new use may present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(B)(ii)(I));
4. The new chemical substance is or will be produced in substantial quantities and either enters or may enter the environment in substantial quantities or there is or may be significant or substantial exposure to the new chemical substance (TSCA §5(a)(3)(B)(ii)(II)); or
5. The new chemical substance or significant new use is not likely to present an unreasonable risk of injury to health or the environment (TSCA §5(a)(3)(C)).

For findings of unreasonable risk, EPA is required to take risk management actions (*e.g.*, consent orders with testing requirements, restrictions on manufacturing, processing, use, disposal, *etc.*) to address unreasonable risks before a company may commence manufacture or processing of the new chemical substance.

EPA reviews all data submitted with a new chemical substance notification; however, unlike laws with prescribed, "up-front" testing requirements (*e.g.*, the Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA), the data requirements for new chemical substance notifications are limited to health or environmental effects in the possession or control of the entity submitting the new chemical substance notification [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>31</RecNum><DisplayText>[1]</DisplayText><record><rec-number>31</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595768685">31</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 720.50 - Submission of test data and other data concerning the health and environmental effects of a substance</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><dates><year>2020</year></dates><pub-location>U.S.</pub-location><urls><related-urls><url>https://www.law.cornell.edu/cfr/text/40/720.50</url></related-urls></urls></record></Cite></EndNote>].

EPA's New Chemicals Program (NCP) has historically used various approaches to evaluate the potential hazards of new chemical substances including ~~the use of~~ computational toxicology models and ~~analogue and~~ category approaches to "read-across" from existing data to new chemical substances for various requisite extrapolations. EPA's TSCA ~~New Chemicals Program~~ (~~NCP~~) developed 56 chemical categories (hereinafter the "NCP Chemical Categories") based on specific ~~chemical~~ definitions and categorical boundaries that summarize the hazard concerns (*e.g.*, human health or environmental toxicity) and recommend testing ~~that may be conducted~~ prior to submitting a new chemical substance notification [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>].

Although the NCP Chemical Categories document provides transparency to the regulated community on the potential concerns that EPA may have for hazards of specific chemistries or physicochemical properties~~to the regulated community on the potential concerns that EPA may have for hazards of specific chemistries or physical properties~~, the NCP Chemical Categories were developed prior to the ~~enactment of the~~ amendments to TSCA, and therefore, do not reflect new vertebrate testing reduction goals [ADDIN EN.CITE <EndNote><Cite><Author>U.S.C.</Author><Year>2016</Year><RecNum>79</RecNum><DisplayText>[3, 4]</DisplayText><record><rec-number>79</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1596122353">79</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S.C.</author></authors></contributors><titles><title>

Title 15-Commerce and Trade, Chapter 53-Toxic Substances Control, Subchapter I-Control of Toxic Substances</title><secondary-title>United States Code (U.S.C.)</secondary-title></titles><periodical><full-title>United States Code (U.S.C.)</full-title></periodical><pages>https://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53&edition=prelim</pages><dates><year>2016</year></dates><urls></urls></record></Cite><Cite><Author>Wheeler</Author><Year>2019</Year><RecNum>80</RecNum><record><rec-number>80</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1596122354">80</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Wheeler, A.R.</author></authors></contributors><titles><title>Directive to Prioritize Effects to Reduce Animal Testing</title><secondary-title>United States Environmental Protection Agency</secondary-title></titles><periodical><full-title>United States Environmental Protection Agency</full-title></periodical><pages>3, https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-231249.pdf</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>]. For example, the testing strategy in the NCP Chemical Categories document for respirable, poorly soluble particulates[1] includes ~~vertebrate animal testing, such as~~ a 90-day subchronic inhalation toxicity study in rats with a 60-day recovery period [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><Dis

[1] EPA identified particles as "respirable" to humans "if there are any particles ≤10 μ[m] in diameter [not otherwise specified, *e.g.*, physical or aerodynamic] in the material being handled by workers" and included "poorly soluble" compounds citing ILSI (2000) [56].

playText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Further, the NCP Chemical Categories cover ~~the~~ defined boundaries ~~defined thereinand therefore~~ may not ~~reflect development of~~include alternative chemistries that are intended to replace a chemical in the ~~do not fit within the~~ current NCP Chemical Categories~~, even for chemicals that the alternative chemistries are intended to replace~~ (*e.g.*, the use of polymeric alternatives to replace monomeric forms of existing chemical substances).

Based on the Agency's experience gained by reviewing over 12,000 polymers, EPA has ~~also~~ developed exemption criteria for specific types of polymeric substances, based on its findings that they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption"~~, for specific types of polymeric substances~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><Dis

playText>[5]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]. New chemical substances meeting these criteria are exempt from the new chemical substance notification requirements, although there are still ~~some requirements, including~~ annual reporting and recordkeeping requirements [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

[PAGE]

EPA's polymer exemption established three polymer exemption types, designated as E1, E2, and E3. The general criteria for new chemical polymer substances meeting these exemption types for polymers are shown in [REF _Ref46665925 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. EPA's exemption criteria for new chemical substances meeting the regulatory definition of a polymer.[a,b]

Exemption Type[a,b]	*Number-average molecular weight (NAMW)*	*Oligomeric Material Criteria*	*Functional Groups (FGs)*[c] *and Functional Group Equivalent Weight (FGEW) Content*
E1	1,000 ≤ NAMW < 10,000	< 10 wt% below 500 Daltons < 25 wt% below	Low concern FGs:[e] no limit Moderate-concern FGs: FGEW ≥ 1,000 Moderate-concern FGs + High concern FGs: $FGEW_{combined}$ ≥ 5,000 High-concern FGs: FGEW ≥ 5,000

[PAGE]

		1,000 Daltons	
E2	NAM W ≥ 10,000	< 2 wt% below 500 Daltons < 5 wt% below 1,000 Daltons	No FG restrictions
E3	No limit	No limit	Polyesters made from one or more of the reactants listed in Table 1 of 40 CFR § 723.250(e)(3) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[a] See 40 CFR § 723.250(b) Polymers. "Polymer means a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least 3 monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. In the context of this definition, sequence means that the monomer units under consideration are covalently bound to one another and form a continuous string within the molecule, uninterrupted by units other than monomer units." [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

[b] The following exclusions apply: Cationic polymers, see 40 CFR § 723.250(d)(1) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; Elemental limitations, see 40 CFR § 723.250(d)(2) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-

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Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]; and Polymers which contain certain perfluoroalkyl moieties consisting of a CF3- or longer chain length, see 40 CFR § 723.250(d)(6) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>].

[c] "These groups are so categorized because they generally lack reactivity in biological settings"; see EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[7]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>]; for discussion, see: EPA (1995) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[5]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type

name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>].

~~As noted, for new chemical substances that meet the polymer exemption criteria, EPA has determined they "will not present an unreasonable risk of injury to human health or the environment under terms of the exemption".~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1995</Year><RecNum>34</RecNum><DisplayText>[5]</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770530">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Premanufacture Notification Exemptions; Revisions of Exemptions for Polymers; Final Rule</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>16316-16336</pages><volume>60</volume><number>60</number><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]~~; however, t~~There are instances, however, where exempt polymers, as well as non-exempt polymeric substances, may be manufactured, processed, used, *etc*., in a manner that may create hazards, which are not intrinsic to the polymer *per se*, but rather ~~are based~~ on the form of the polymer (*e.g.*, respirable). For example, high-molecular weight (HMW) polymers (*i.e.*, NAMW $\geq$ 10,000 Daltons) that meet the E2 criteria and are manufactured or used as particles with sizes in the respirable range (*i.e.*, $\leq$ 10 µm) represent a ~~general~~ class of chemical substances (hereinafter referred to as "HMW polymers") that may cause anpotential inhalation ~~toxicity~~ hazards, including~~(*i.e.*,~~ lung overload[2]~~)~~ *via* ~~the~~ a

[2] Overload is defined in this article as when the exposure concentration is sufficiently high or the duration sufficiently long to overwhelm AM-mediated clearance.

specific mode~~(s)~~ of action (*i.e.*, impairment of alveolar-macrophage [AM] mediated clearance), as identified in rat inhalation studies, ~~to~~ within chemical substances present in the respirable, poorly soluble particulates ~~in the~~ NCP Chemical Categor~~ies document for respirable, poorly soluble particulatesy~~. The focus on overload has been due to the fact that poor soluble particles appear to produce lung tumors in rats when AM-mediated clearance is over-whelmed and chronic inflammation is present. However, the chemical substances that are provided as analogues ~~within the boundaries for the~~ within the boundaries for the NCP Chemical Category on respirable, poorly soluble particulates are limited to discrete inorganic substances, including oxides of various metals (*e.g.*, titanium dioxide) or nonmetals (*e.g.*, carbon black). In contrast, HMW polymers consist of the polymeric substance, as well as varying weight fractions of oligomeric material (*e.g.*, < 5 wt% below 1,000 Daltons for ~~those~~ polymers meeting the E2 criteria).

The purpose of the present evaluation was to perform a systematic review of the literature to identify available information that would support: (1) establishing physicochemical boundaries for a chemical category on HMW polymers; (2) determining whether specific chemical substances could be used as ~~representative~~ a first step with ~~toxicological analogues with~~identifying points of departure for the members of this category; and (3) establishing a proposed tiered-testing strategy for evaluating new chemical substances that meet the chemical boundaries for this category. ~~An additional aim was to introduce~~In addition, a new approach ~~methodologies~~ methodology (NAMs) was introduced as a~~the~~ tiered-testing strategy ~~to~~ that meets the statutory mandate under TSCA to reduce or replace the use of vertebrate animals in the testing of chemical substances.

MATERIALS AND METHODS

Systematic Literature Review

An initial literature search was conducted in November 2016, and a supplemental literature search was conducted in April 2018. The details of these reviews, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcomes (PECO) criteria used for reviewing results for relevance are provided in the Supporting Information file at "Section 1 Systematic Literature Review". The objective of these reviews was to obtain studies that evaluated potential "lung overload" toxicity, *i.e.*, respiratory tract toxicity of HMW polymers in exposed humans, investigated lower respiratory tract (*i.e.*, the tracheobronchial and alveolar regions) effects in laboratory animals and identified points of departure, or informed the mode of action for these agents at a cellular level (*i.e.*, *in vitro* studies). In the context of this evaluation, "lung overload" refers to the "type of retained lung burden seen with excessively high exposures [in rodents] that lead to impairment of AM [alveolar macrophage]-mediated particle clearance" [ADDIN EN.CITE <EndNote><Cite><Author>Miller</Author><Year>2000</Year><RecNum>37</RecNum><DisplayText>[8]</DisplayText><record><rec-number>37</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595773878">37</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author></authors></contributors><auth-address>Chemical Industry Institute of Toxicology, 6 Davis Drive, PO Box 12137, Research Triangle Park, NC 27709, USA. fmiller@ciit.org</auth-address><titles><title>Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload

and human health risk assessment: a critical review</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>19-57</pages><volume>12</volume><number>1-2</number><edition>2000/03/15</edition><keywords><keyword>Air Pollutants/*adverse effects/pharmacokinetics</keyword><keyword>Air Pollutants, Occupational/*adverse effects/pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Animals, Laboratory</keyword><keyword>Body Burden</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Humans</keyword><keyword>Lung/*drug effects/metabolism</keyword><keyword>Pneumoconiosis/*etiology/metabolism</keyword><keyword>Risk Assessment</keyword><keyword>Species Specificity</keyword></keywords><dates><year>2000</year><pub-dates><date>Jan-Feb</date></pub-dates></dates><isbn>0895-8378 (Print)
0895-8378</isbn><accession-num>10715617</accession-num><urls></urls><electronic-resource-num>10.1080/089583700196536</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Since "overload" is ~~defined~~ manifest differently in experimental animals versus humans [ADDIN EN.CITE ADDIN EN.CITE.DATA], the literature searches used search strings that were intended to be overly inclusive to identify studies that evaluated "overload" in both experimental animals and humans. A secondary objective was to ~~identify~~ develop ~~potential NAMs that may be incorporated into~~ a tiered-testing strategy that minimizes the use of vertebrate animals and can serve as a NAM for this chemical category.

[PAGE]

Risk Assessment Approaches Under TSCA

EPA generally uses ~~the~~ a margin of exposure (MOE) approach for quantifying potential non-cancer risks in risk assessments ~~performed~~ on new chemical substances ~~under TSCA~~. The MOE ~~approach~~ is calculated based on a point(s) of departure (POD) divided by ~~a~~ the human exposure estimate(s). The POD is ~~typically identified~~developed from an effect level ~~from a study(ies) in experimental animals~~ (*e.g.*, no-observed-adverse-effect concentration [NOAEC], lowest-observed-adverse-effect concentration [LOAEC], or by performing benchmark dose modeling~~benchmark dose [BMD])~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 15]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-

id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. An ~~duration~~ adjustment is applied to the POD to account for the exposure conditions under evaluation (*e.g.*, workers = 8 hours/day, 5 days/week) versus the exposure conditions ~~employed~~ in the experimental study (*e.g.*, 6 hours/day, 5 days/week). The human exposure estimate is typically generated ~~for new chemical substances~~ using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as acute potential dose rates (PDRs) ~~in mg/day~~ or lifetime average daily doses (LADDs) ~~in mg/kg-bw/day~~. Given that most new chemical substances ~~will~~ usually do not have occupational exposure monitoring data, ~~except for possible monitoring data on analogues,~~ the PDR is ~~typically~~ used as an initial conservative exposure estimate when calculating the MOE. For chemical substances ~~used~~ in a powder or particulate form, the ~~general~~ default PDR values for respirable ~~or~~ and total particulates are 50 mg/day (*i.e.*, 5 mg/m^3) ~~or~~ and 150 mg/day (*i.e.*, 15 mg/m^3), respectively [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>44</RecNum><Dis

playText>[16]</DisplayText><record><rec-number>44</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595776956">44</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>ChemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>399</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. However, for chronic effects ~~like~~ including lung overload, the LADD represents the more appropriate exposure metric for quantifying potential risks [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2013</Year><RecNum>45</RecNum><DisplayText>[17]</DisplayText><record><rec-number>45</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595778575">45</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Interpretive Assistance Document for Assessment of Discrete Organic Chemicals, Sustainable Futures Summary Assessment</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</full-title></periodical><pages>20, https://www.epa.gov/sites/production/files/2015-05/documents/05-iad_discretes_june2013.pdf</pages><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]. A summary of the default values used ~~for~~ in calculating PDRs and LADDs for new chemical substances in powder or particulate form is provided in [REF _Ref46666189 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. Default values used for calculating the PDR and LADD.

Description	Equation	Parameter	Defaults	Units
PDR (mg/day)	Cm × b × h	Mass concentration of chemical in air (Cm)	5	mg/m^3
		Volumetric inhalation rate (b) ($0 < b \leq 7.9$)	1.25	m^3/hr
		Exposure duration (h) ($0 \leq h \leq 24$)	8	hrs/day
LADD[a] (mg/kg-bw/day)	(I × ED × EY) / (BW × ATc × 365 days/yr)	Inhalation PDR (I)	50	mg/day
		Days exposed per year (ED) ($0 \leq$ ED (integer) ≤ 365)	250	days/site-yr
		Years of occupational exposure (EY) ($0 \leq$ EY)	40	years
		Body weight (BW) ($0 \leq$ ATc)	80	kg
		Averaging time over a lifetime (chronic) ($0 \leq$ ATc)	70	years

[a] Note, dosimetric modeling may be applied using models such as Multipath Particle Dosimetry (MPPD) to perform simulations. These simulations may be adjusted to account for the days exposed per year, and when evaluating the years of occupational exposure, preclude the need for averaging exposures over a specified time period (*e.g.*, lifetime) because these types of adjustments are incorporated into the construction of the human equivalent concentration (HEC).

For each of the MOEs calculated ~~herein~~in this article, both the PDR and LADD have been provided ~~are provided~~ for comparison. The resulting MOE is compared to a benchmark MOE for characterizing potential risks. If the MOE is lower than the benchmark MOE, potential risks are indicated under TSCA, whereas if the MOE is higher than the benchmark MOE, the ~~risks are not considered a concern under TSCA~~chemical substance is considered as not posing a potential risk.

Benchmark MOE Derivation

The benchmark MOE ~~is derived to~~ accounts for both uncertainty and variability. In the context of this article, these terms have the same meaning as defined by EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192,

https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] and are based on the following considerations: intraspecies (a.k.a., intrahuman) variability (*i.e.*, human-to-human variability or UF_H), interspecies variability (*i.e.*, animal-to-human extrapolation uncertainty or UF_A), and LOAEC-to-NOAEC uncertainty (*i.e.*, uncertainty with extrapolating from a Lowest Observed Adverse Effect Concentration [LOAEC] to a No Observed Adverse Effect Concentration [NOAEC] or UF_L). The default UF values used for calculating the benchmark MOE are 10 for each of the composite uncertainty factors (*i.e.*, $UF_H \times UF_A \times UF_L = 1000$). EPA has developed guidance ~~focused on improving~~to improve the science underlying the animal-to-human uncertainty factor, which provides generalized procedures for deriving dosimetric adjustment factors (DAF), which are applied to adjust exposure levels of observed toxicity in the animals and perform interspecies extrapolation [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 18]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-

final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. As described below in the section on interspecies extrapolation and overload simulations, ~~Application~~ application of DAFs to the animal airborne exposure values yields estimates of the concentration ~~that would result in the same concentration to~~in humans, ~~that is,~~ the Human Equivalent Concentration (HEC). For studies ~~reporting~~ with only a LOAEC, EPA recommends benchmark dose modeling be performed~~, if the experimental data are amenable,~~ to identify a benchmark dose lower limit value (BMDL), as described in the next section, and thereby reduce the LOAEL-to-NOAEL UF value to 1. Each of these adjustments is discussed below, along with

their potential applicability to the available studies that evaluated lung overload from HMW polymers.

Benchmark Dose Modeling

Commented [ST1]: Annie recommended moving this section. I accepted the move, so her edits can be seen

EPA's benchmark dose modeling ~~(BMD)~~ software (BMDS) is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. When a NOAEC is not available in a study, EPA typically applies a UF_L of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the UF_L may be reduced from 10 to 1 ~~. The statistical lower confidence limit on the concentration at the BMD (*i.e.*,~~because the BMDL~~)~~ is a dose level corresponding to specific response levels near the low end of the observable range of the data ~~that~~ and incorporates and conveys more

information than the NOAEC or the LOAEC [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. EPA's BMD software (BMDS, ver. 3.1.1) was used for dose-response modeling of dichotomous (*e.g.*, lesion incidence) data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was selected, model fit evaluated using the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals at concentrations near the BMR, and visual assessment of the model fit as displayed graphically. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit, per EPA's guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

Interspecies Extrapolation and Dosimetry Simulations Demonstrating Overload

Commented [JA2]: Needed context for why the two models were being used and to connect with the benchmark MOE section. Otherwise really hard to follow.

Commented [ST3R2]: Note, Annie added this section. I accepted it, so you could see any edits, I may make

It has long been recognized that the external exposure concentration of particles is not the same amount that is inhaled, subsequently deposited and retained, and responsible for potential adverse health effects. -Inhaled dose is dictated by particle inhalability and deposition mechanisms that can display regional and anatomical differences in the respiratory tract of experimental animals and humans at different ages~~relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages~~. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation tidal volume and breathing rate; and ~~as well interact with~~by key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the

integrated processes of inhalability, deposition, and clearance. -Dosimetry[3] models have been used for decades to describe the physicochemical and biological determinants of aerodynamic behavior and toxicological responses of inhaled particles. -Such models are applied to account for species differences in the complex interactions among the described physicochemical, anatomical and physiological factors to determine inhaled dose metrics relevant to the ~~mode of action~~ (MOA) [ADDIN EN.CITE <EndNote><Cite><Author>Jarabek</Author><Year>2005</Year><RecNum>81</RecNum><DisplayText>[19]</DisplayText><record><rec-number>81</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1596125766">81</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Jarabek, A. M.</author><author>Asgharian, B.</author><author>Miller, F. J.</author></authors></contributors><auth-address>National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA.</auth-address><titles><title>Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles (PSP)</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>317-34</pages><volume>17</volume><number>7-8</number><edition>2005/07/16</edition><keywords><keyword>Air

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[3] Dosimetry refers to measuring or predicting the amount (*e.g.*, mass, surface area or number) of particles in a specific region of the respiratory tract at a particular point in time. Dose metrics, *e.g.*, deposited or retained mass in a specific region of the respiratory tract normalized to its surface area for portal-of-entry effects, should be constructed to correspond to the MOA of the particle and the observed toxic effect of interest.

Pollutants/*toxicity</keyword><keyword>Animals</keyword><keyword>Humans</keyword><keyword>*Inhalation Exposure</keyword><keyword>*Models, Theoretical</keyword><keyword>Particle Size</keyword><keyword>Reference Values</keyword><keyword>Reproducibility of Results</keyword><keyword>Risk Assessment</keyword><keyword>Toxicity Tests</keyword></keywords><dates><year>2005</year><pub-dates><date>Jun-Jul</date></pub-dates></dates><isbn>0895-8378 (Print)
0895-8378</isbn><accession-num>16020031</accession-num><urls></urls><electronic-resource-num>10.1080/08958370590929394</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. ~~-~~Herein, we explore two different available dosimetry models and conduct simulations to demonstrate factors determining overload.

Regional ~~Dose~~ Deposited ~~Dosimetry~~ Dose Ratio (RDDR) Model (U.S. EPA, 1994)

EPA introduced formal dosimetry modeling into its derivation procedures for risk assessment of inhaled materials with its ~~EPA may apply DAFs to PODs identified from experimental animal studies based on the methods described in its~~ 1994 ~~guidance~~ document entitled ~~titled~~ "*Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

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timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. ~~When applied~~As described above, EPA may apply DAFs to PODs identified from experimental animal studies to calculate an HEC. When applied, the default DAF accounts for the toxicokinetic component of the UF_A and it is thereby reduced from approximately 3 (*i.e.*, $10^{0.5}$) to 1, ~~since~~ the POD is dosimetrically adjusted to a POD_{HEC}, ~~whereas~~and the ~~remaining~~ UF_A value of approximately 3 accounts for the toxicodynamic component of the UF_A. ~~Dosimetry or physiologically-based pharmacokinetic models are preferred to the default models when they are available.~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation

Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

To derive a DAF for particle exposures, EPA developed a software program for calculating the regional deposited dose ratio (RDDR), ~~that is,~~ as the DAF for insoluble particles. The RDDR is an empirical model of deposition, ~~that is~~ applicable to particles in the size range of 0.5-30 μm and calculates an RDDR ~~value~~ as the DAF for insoluble particles using the following ratios:

$$RDDR = \frac{V_{E,animal}}{V_{E,human}} \times \frac{F_{r,animal}}{F_{r,human}} \times \frac{NF_{human}}{NF_{animal}}$$

These ratios incorporate animal to human adjustments for the following parameters: minute volume (V_E; mL/min), depositional fraction (Fr) ~~of the particulate in the~~ of the particle in the regions of respiratory tract (*i.e.*, extrathoracic, tracheobronchial, and pulmonary), and a normalizing factor (NF), such as respiratory tract surface area of the region with the observed toxicity for portal-of-entry effects, ~~for the region of interest~~. The RDDR ~~user~~ inputs include mass median aerodynamic diameter (MMAD), geometric standard deviation (σ) ~~for the particle of interest~~, and the average bodyweight of the animal ~~used in the study~~ from which default V_E and

surface areas of the respiratory tract regions ~~for the animal~~ are calculated. Human ventilatory parameters and assumptions regarding exposure regimen (*e.g.*, hours/day and lifetime) are analogously used in the model to predict the human deposition fraction with default values for the NF. The RDDR ~~may be~~is applied to the ~~duration~~ duration-adjusted POD, which describes the ~~; however, risk assessments performed under TSCA apply the RDDR to the POD obtained under the~~ laboratory animal regimen, to arrive at the POD_{HEC}. Thereafter, the duration adjustment is applied when quantifying the MOE for the population of interest. The RDDR software (version 2.3) was run with the assistance of DOSBox, an open-source and free DOS-emulator [ADDIN EN.CITE <EndNote><Cite><Author>DOSBox</Author><Year>2019</Year><RecNum>48</RecNum><DisplayText>[20]</DisplayText><record><rec-number>48</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789343">48</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>DOSBox</author></authors></contributors><titles><title>DOSBox "Way more FPA than Counterstrike !"</title></titles><pages>https://www.dosbox.com/</pages><dates><year>2019</year></dates><urls></urls></record></Cite></EndNote>].

Multiple-Path Particle Dosimetry (MPPD) Model

~~Inhaled dose is dictated by inhalability and deposition mechanisms that differ in relative contribution for each region of the respiratory tract as well as differ due to the anatomical differences between experimental species and humans at different ages. These deposition mechanisms are also influenced by the breathing mode (*e.g.*, oral, nasal, or both), the ventilation~~

~~tidal volume and breathing rate; and as well interact with key physicochemical properties of aerosols including particle size, distribution, density, and hygroscopicity. Clearance mechanisms include dissolution, mucociliary removal, and translocation to the alveolar (pulmonary) interstitium. Retained dose is a function of the integrated processes of inhalability, deposition, and clearance.~~

The Multiple-Path Particle Dosimetry (MPPD) model (version 3.04) developed by Anjilvel and Asgharian (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Anjilvel</Author><Year>1995</Year><RecNum>73</RecNum><DisplayText>[21]</DisplayText><record><rec-number>73</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839173">73</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Anjilvel, S.</author><author>Asgharian, B.</author></authors></contributors><auth-address>Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.</auth-address><titles><title>A multiple-path model of particle deposition in the rat lung</title><secondary-title>Fundam Appl Toxicol</secondary-title><alt-title>Fundamental and applied toxicology : official journal of the Society of Toxicology</alt-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>41-50</pages><volume>28</volume><number>1</number><edition>1995/11/01</edition><keywords><keyword>Airway Resistance/physiology</keyword><keyword>Animals</keyword><keyword>Bronchi/anatomy & histology/physiology</keyword><keyword>Lung/*anatomy &

histology/physiology</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Respiratory Function Tests</keyword><keyword>Respiratory Mechanics/physiology</keyword><keyword>Tidal Volume/physiology</keyword><keyword>Trachea/anatomy & histology/physiology</keyword></keywords><dates><year>1995</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590</isbn><accession-num>8566482</accession-num><urls></urls><electronic-resource-num>10.1006/faat.1995.1144</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and updated by Miller *et al.* (2016) [ADDIN EN.CITE <EndNote><Cite><Author>Miller</Author><Year>2016</Year><RecNum>70</RecNum><DisplayText>[22]</DisplayText><record><rec-number>70</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838679">70</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Miller, F. J.</author><author>Asgharian, B.</author><author>Schroeter, J.D.</author><author>Price, O.</author></authors></contributors><titles><title>Improvements and additions to the Multiple Path Particle Dosimetry model</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>14-26</pages><volume>99</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] is a mechanistic, multipath model that ~~was modified and~~can be used to

predict deposition, clearance, and retained lung burden over the course of a long-term exposure , as described by Ladics *et al.* (2020) [ADDIN EN.CITE <EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[23]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD model is supported by Applied Research Associates, Inc. (ARA) and is available as freeware. An EPA version of MPPD is anticipated to undergo external peer review for application to Agency assessments late FY20. As with the RDDR ~~outputs~~model, the MPPD ~~outputs~~ model provides ~~values~~ predictions that may be used to calculate a POD_{HEC} for inhaled deposited dose; however, unlike the RDDR model, the MPPD model additionally provides ~~outputs~~ predictions of retained dose that may be more appropriate to characterize chronic effects. ~~used to characterize acute exposures *via* deposition and subchronic/chronic exposures *via* retained dose.~~The MPPD model also incorporates inhalability[4], covers a wider size range of

[4] Inhalability can be defined as the probability that a particle of a given size will actually enter one of the

particles (0.01 – 100 µm), and has other added capabilities including the ability to construct simulations of activity patterns with different ventilation parameters within a given day.

To calculate clearance and thereby retained dose, ~~The~~ the MPPD model (version 3.04) uses default translocation rates in the alveolar interstitium that were recommended by the International Commission on Radiological Protection (ICRP) in their 1994 human respiratory tract model [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models,

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respiratory tract orifices in the case of non-human primates or humans or enter the nares in the case of rodents that are obligatory nose breathers. Inhalability varies between species and is a critical adjustment for interspecies extrapolation.

Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. These rates are considered representative of insoluble particles. More recently, the ICRP model and clearance rates have been updated based on improved lung burden data [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Refinements may be imparted by chemical-specific dissolution data and exploration of these new model values. Hygroscopic growth is currently not addressed in either the MPPD or ICRP models; and is not likely to be relevant to this category of inhaled polymers. In rats, MPPD implements a two-compartment pulmonary clearance model where the alveolar clearance rate decreases as alveolar retained mass increases. MPPD predicts the alveolar clearance rate based on an empirical model fit to titanium dioxide retained mass data from 13-week rat exposures. In humans, MPPD implements the ICRP clearance model localized for individual airways in the pulmonary region. Clearance rates in the ICRP human clearance model are constant and do not vary with alveolar retained mass. Therefore, depression of clearance rates associated with lung overload is incorporated in the MPPD rat model, but not the MPPD human

model. Additional uncertainty in the predictions is imparted from the use of lung geometry models for different rat species than used in the experiment, but nonetheless will be shown to fit experimental data well.

Benchmark Dose Modeling

EPA's benchmark dose modeling (BMD) software is routinely used for evaluating datasets because of its advantages over using the NOAEC/LOAEC approach, as discussed in EPA (2012) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. When a NOAEC is not identified in a study, EPA typically applies a UF_L of 10 to extrapolate from the LOAEC to the NOAEC. However, when datasets are amenable to BMD modeling, the UF_L may be reduced from 10 to 1, because the BMDL is a dose level corresponding to specific

~~response levels near the low end of the observable range of the data and incorporates and conveys more information than the NOAEC or the LOAEC~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. ~~EPA's BMD software (BMDS, 3.1.1) was used for dose-response modeling of dichotomous (*e.g.*, lesion incidence) data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was selected, and model fit was evaluated using the $\chi 2$ goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals at concentrations near the BMR, and visual assessment of the model fit as displayed graphically. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit, per EPA's guidance~~ [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

RESULTS AND DISCUSSION

Literature Search and Screening Results

The initial literature search identified 257 articles on PubMed. Following title and abstract screening, 28 articles were selected for full text review, and 23 articles were identified using additional search strategies (*e.g.*, tree searching). Of the 51 articles identified for full text review, only 24 articles contained relevant information that satisfied the PECO criteria for lung overload from HMW polymers. In the supplemental literature search, 1218 articles were identified on PubMed and Embase (combined). Title and abstract screening resulted in 46 potentially relevant articles for full text screening. Of these, 13 were identified as potentially relevant for review; seven of the 13 articles were also identified in the initial literature search. Complete details on the

systematic review are provided in the Supporting Information file at "Section 1 Systematic Literature Review".

The information identified in the systematic review was used to inform the inclusion/exclusion criteria in the section on Category Boundaries, to develop the health effects summaries in the section on Hazard Identification, and to identify NAMs to include in the section on Tiered-Testing Strategies.

Category Boundaries

The ~~category~~ boundaries for HMW polymers that may present a hazard for lung overload include those that do not meet the exclusion criteria listed under EPA's polymer exemption at 40 CFR § 723.250(d) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>35</RecNum><DisplayText>[6]</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595770827">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>40 CFR § 723.250 - Polymers</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/723.250</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], are respirable (*i.e.*, manufactured, processed, or used in a respirable form), non-reactive, and poorly soluble. Each of these boundary criteria, except for EPA's polymer exclusion criteria, is discussed ~~further~~ below.

It should be noted that even if a HMW polymer satisfies the ~~category~~ boundary criteria for the category, there may be other hazards under the conditions for use of the chemical substance due to low molecular weight components, residuals, impurities, and/or potential metabolites that are considered, and may ultimately be the critical effect, used to quantify risks.

In humans, ~~Respirable~~ respirable particles are those chemical substances with an aerodynamic particle size of less than or equal to 10 μm. The cutoff of 10 μm, as defined by EPA in its "*Air Quality Criteria for Particulate Matter*", represents "particles collected by a sampler with an upper 50% cut point of 10 μm D_a [aerodynamic diameter] and a specific, fairly sharp, penetration curve" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[26]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndN

ote>]. However, depending on the sampling method and size fraction collected, the sample may contain particles between 10 and 30 μm diameter that are excluded from the 10 μm D_a fraction [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2004</Year><RecNum>50</RecNum><DisplayText>[26]</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595790424">50</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume I of II</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>900, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=435945</pages><volume>EPA/600/P-99/002aF</volume><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>].

In comparison, occupational health organizations rely on unified size fraction definitions based on the upper size ~~cuts~~ of particles and entry into the different regions of the respiratory tract. For example, the American Conference of Governmental Industrial Hygienists (ACGIH) considers 10 μm D_a particles as an upper limit for particles ~~with this size~~ entering the alveolar region [ADDIN EN.CITE

<EndNote><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><DisplayText>[27]</DisplayText><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Further, consideration must ~~also~~ be given to the particle settling ~~that may occur~~rate. ~~For example,~~ ~~i~~In still air, 10 μm spherical particles with a density of 1 g/cm^3 can remain airborne for approximately 8 minutes [ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[28]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute

for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. ~~However~~, and as particle size decreases, the airborne settling time increases (*e.g.*, approximately 1.5 hours for 3 μm particles to settle in still air) [ADDIN EN.CITE <EndNote><Cite><Author>Baron</Author><Year>2004</Year><RecNum>53</RecNum><DisplayText>[27, 28]</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791478">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Baron, P.</author></authors></contributors><titles><title>Generation and Behavior of Airborne Particles (Aerosols)</title><secondary-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</secondary-title></titles><periodical><full-title>Division of Applied Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention</full-title></periodical><pages>40, https://www.cdc.gov/niosh/topics/aerosols/pdfs/aerosol_101.pdf</pages><dates><year>2004</year></dates><urls></urls></record></Cite><Cite><Author>ACGIH</Author><Year>1999</Year><RecNum>52</RecNum><record><rec-number>52</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1595791048">52</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ACGIH</author></authors></contributors><titles><title>Particle Size-Selective Sampling for Health-Related Aerosols</title><secondary-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</secondary-title></titles><periodical><full-title>American Conference of Governmental Industrial Hygienists, Air Sampling Procedures Committee, Ed. Vincent, J.H.</full-title></periodical><pages>240, https://www.acgih.org/forms/store/ProductFormPublic/particle-size-selective-sampling-for-particulate-air-contaminants</pages><volume>ISBN 1-1882417-30-5</volume><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]. Therefore, solids with even a small fraction of respirable particles may produce prolonged and elevated airborne levels of respirable particles in the workplace. ~~Though~~ Although occupational monitoring data provide ~~the most direct~~ assurance that airborne levels of respirable particles do not exceed relevant exposure limits, particle size distribution data are typically the only metric available for estimating potential respirability for new chemical substances. Given this limitation and ~~the reality~~ that ~~nearly all~~ solid particulate materials may contain some percentage of respirable particles, a practical screening cutoff is warranted for category inclusion/exclusion.

For the purposes of defining this category, we propose that HMW polymers are considered respirable if they are manufactured, processed, used, *etc.*, in a manner that generates the new chemical substance with a particle or aerosol size of less than or equal to 10 μm or if respirable particles may be unintentionally generated during the life cycle of the material (*e.g.*, impaction and friction during transport). Under the latter scenarios, ~~a practical cutoff of~~ >materials that

contain greater than or equal to 1% respirable particles by weight (wt%) based on particle size distribution data is the practical ~~as the~~ cutoff for assessing respirable particles and ~~this percentage would be based on particle size distribution data for the material. The practical cutoff of ≥ 1 wt%~~ is the same cutoff EPA applies to the nonreportable content of nanoscale materials [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2017</Year><RecNum>54</RecNum><DisplayText>[29]</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595791830">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping Requirements</title><secondary-title>Federal Register</secondary-title></titles><periodical><full-title>Federal Register</full-title></periodical><pages>3641-3655</pages><volume>82</volume><number>8</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ~~This~~ The same cutoff would apply to the particle/droplet size distribution ~~in the case of~~for aerosols of a solid or liquid chemical substance and would be determined based on droplet size data for the material and/or liquid application method (*e.g.*, spray, aerosol, mist).

Commented [ST4]: There were previous edits from EPA, but not Annie. This seems awkward to me. I think the original text was clearer. Thoughts?

Another option is: "respirable particles that are greater than or equal to 1% by weight (wt%) based on particle size distribution data for the material is the practical inclusion cutoff for assessing respirable particles and is the same cutoff EPA applies to the nonreportable content of nanoscale materials"

EPA's Functional Group (FG) and Functional Group Equivalent Weight (FGEW) criteria for E1 polymers provide a starting point for evaluating the potential reactivity and/or cytotoxicity of HMW polymers. Therefore, we propose using these criteria as an initial screen for determining whether a HMW polymer is considered non-reactive and included or reactive and ~~included or~~

excluded from the category~~, respectively~~. As shown in [REF _Ref46665925 \h * MERGEFORMAT], the E1 polymer exemption criteria include low-concern, moderate-concern, or high-concern FGs. ~~A summary of r~~Representative FGs meeting each of these hazard concern levels is shown in [REF _Ref46674358 \h * MERGEFORMAT].

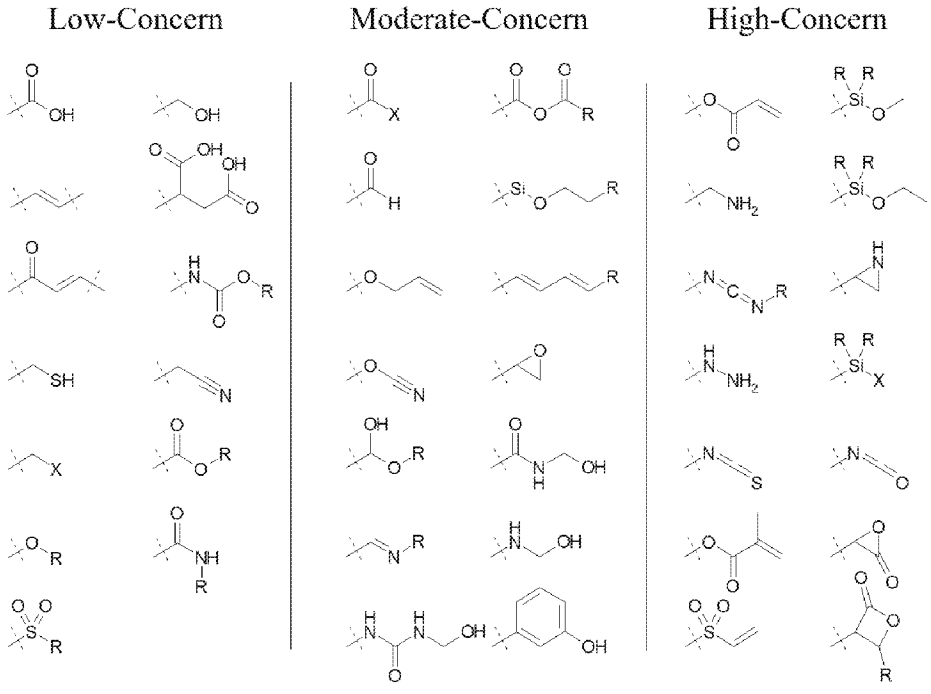


Figure [SEQ Figure * ARABIC]. FG hazard concern levels for polymeric substances meeting EPA's E1 polymer exemption criteria. The FGs shown above are representative alerts for identifying a HMW polymer as non-reactive (low concern)/reactive (moderate or high concern) for the HMW polymer category. The following cutoffs are proposed as the category boundaries for establishing that a HMW polymer is non-reactive: low-concern FGs (no limit), moderate-

concern FGs (FGEW ≥ 1,000), or high-concern FGs (FGEW ≥ 5,000). "R" represents an undefined structure; "X" represents a halide. See: EPA (1997) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1997</Year><RecNum>36</RecNum><DisplayText>[7]</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595771575">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Polymer Exemption Guidance Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>54, https://www.epa.gov/sites/production/files/2015-03/documents/polyguid.pdf</pages><volume>EPA 744-B-97-001</volume><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] for further details.

A ~~generally recognized~~ property of respirable, low reactive (*i.e.*, low toxicity) particles that ~~can~~ may cause lung overload is the poorly soluble nature of these compounds. EPA has published general water solubility classifications, which include: negligible solubility (*i.e.*, < 0.1 mg/L), slight solubility (*i.e.*, > 0.1 - 100 mg/L), moderate solubility (*i.e.*, > 100 - 1,000 mg/L), soluble (> 1,000 - 10,000 mg/L), and very soluble (> 10,000 mg/L) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>56</RecNum><DisplayText>[30]</DisplayText><record><rec-number>56</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792442">56</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Section 5. Estimating Physical/Chemical and Environmental Fate Properties with EPI SuiteTM, Sustainable Futures/P2 Framework Manual</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>22, https://www.epa.gov/sites/production/files/2015-05/documents/05.pdf</pages><volume>EPA-748-B12-001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. These values were not established for evaluating the solubility of particles for lung overload; however, they may be used as conservative cutoffs for extractability, per OECD TG 120 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2000</Year><RecNum>55</RecNum><DisplayText>[31]</DisplayText><record><rec-number>55</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595792078">55</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Solution/Extraction Behaviour of Polymers in Water</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>4, https://www.oecd-

ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-1-physical-chemical-properties_20745753</pages><volume>120</volume><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>], for measuring the insolubility/solubility of HMW polymers. ECETOC (2013) [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>] proposed an initial biosolubility screening approach that provided qualitative determinants (*i.e.*, "soluble", "insoluble", "Low dissolution rate", or "Very high dissolution rate") for assessing biosolubility; however, no quantitative thresholds were provided. In comparison, the International Commission on Radiological Protection (ICRP) and the German Federal Institute for Occupational Safety and

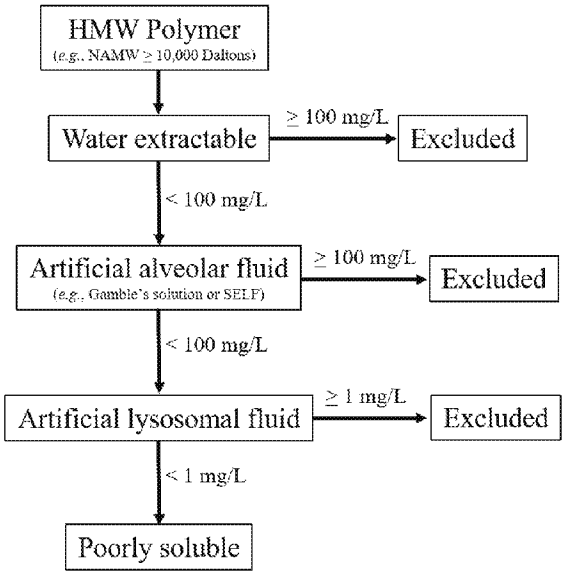
Health (FIOSH) provided quantitative biosolubility cutoffs. ICRP describes three categories of soluble radiological materials: Fast (all material rapidly dissolves at a rate of 100 day^{-1}), Moderate (10% of the material dissolves rapidly and the rest dissolves at a rate of 0.005 day^{-1}), and Slow (0.1% of the material dissolves rapidly and the rest dissolves at a rate of 0.0001 day^{-1}) [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract

Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. FIOSH proposed a simulated solubility threshold of ≤ 1 mg/L in artificial lung fluids for identifying particles as "low soluble dusts" [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[33]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

As discussed ~~previously~~above, the screening particle size cutoff and percentage of respirable particles for inclusion in this HMW polymer category are ≤ 10 μm and ≥ 1 wt%, respectively. These criteria are readily determinable based on the intended use and life cycle of the HMW

polymer. However, determining whether a HMW polymer is "poorly soluble" and a potential hazard concern for lung overload is also dependent on the potential daily exposure estimates. Therefore, we propose using the inclusion/exclusion cutoffs shown in [REF _Ref46673847 \h * MERGEFORMAT], which consider water extractability~~/~~ or biosolubility and the legally binding permissible exposure limit (PEL), as mandated by the U.S. Occupational Safety and Health Administration (OSHA) for respirable particulates not otherwise regulated ~~or~~ (PNOR) (*i.e.*, 5 mg/m^3).

Scheme [SEQ Scheme * ARABIC]. Screening criteria for determining water extractability and biosolubility.

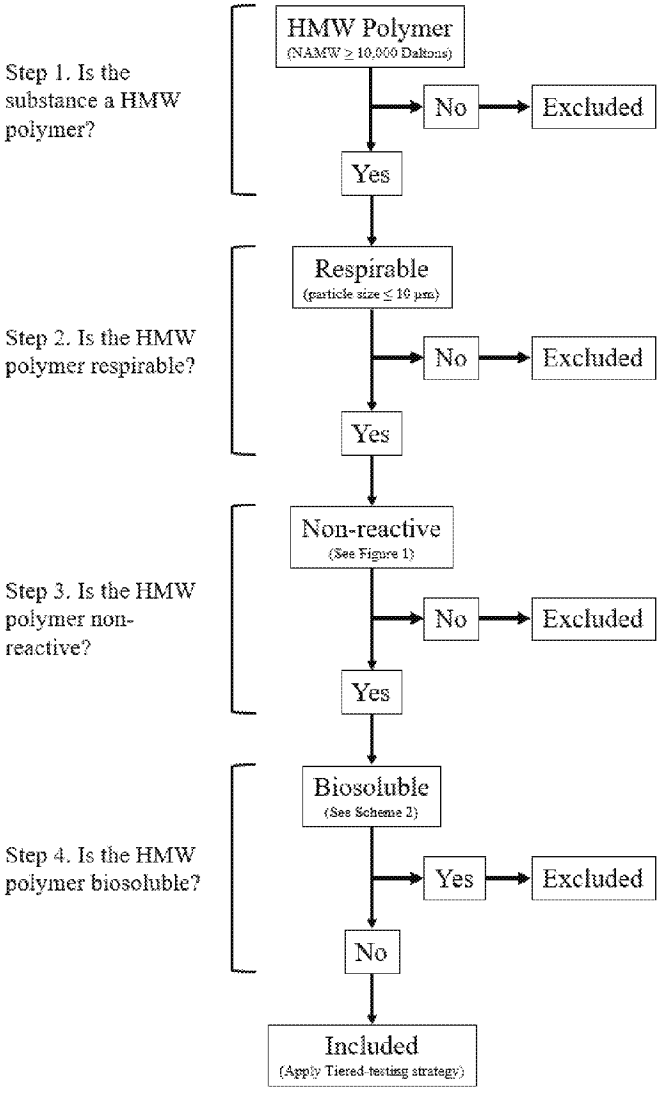


The proposed cutoffs shown in Scheme 1 are based on the following considerations. The first ~~screen~~ step is water extractability using the cutoff for moderately water-soluble substances. While the screen is intended to identify insoluble (*i.e.*, non-extractable) HMW polymers, the EPA water solubility classifications were not specifically established to identify potential hazards related to lung overload and have not been ~~established to correlate~~correlated with either biosolubility or biopersistence. Therefore, EPA's cutoff for moderate water solubility (*i.e.*, 100 mg/L) was selected ~~rather than the low water solubility cutoff~~, since it ~~represents a transition from slight to moderate water solubility and~~ is ~~therefore~~ expected to be conservatively inclusive ~~in the first step because water extractability is generally expected~~and to overestimate the insolubility of polymers in biological fluids. In the second ~~screen~~step, ~~two~~ biosolubility cutoffs ~~may be used,~~are either 100 mg/L or 1 mg/L, depending on the test system used (*e.g.*, simulated epithelial lung fluid or artificial alveolar macrophage lysosomal fluid). These values account for the biosolubility of the HMW polymer, as well as the OSHA PNOR PEL of 5 mg/m^3 (*i.e.*, 50 mg/day; 5 mg/m^3 × 10 m^3/day) for the respirable fraction, defined based on size selective characteristics as particles smaller than 10 µm aerodynamic diameter. The ~~first value is based on EPA (2020) where the Agency applied a~~ biosolubility cutoff of approximately 100 mg/L/day for a polymer in simulated epithelial lung fluid. ~~This value would~~ equates to a mean dissolution rate of approximately 72 mg/day in humans, based on an estimated daily alveolar fluid turnover of 0.72 L [ADDIN EN.CITE <EndNote><Cite><Author>Fronius</Author><Year>2012</Year><RecNum>58</RecNum><DisplayText>[34]</DisplayText><record><rec-number>58</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595795295">58</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Fronius, M.</author><author>Clauss, W.G.</author><author>Althaus, M.</author></authors></contributors><titles><title>Why do we have to move fluid to be able to breath?</title><secondary-title>Frontiers in Physiology</secondary-title></titles><periodical><full-title>Frontiers in Physiology</full-title></periodical><pages>5, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357553/pdf/fphys-03-00146.pdf</pages><volume>3</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The second value is based on the German FIOSH biosolubility cutoff of 1 mg/L for granular biopersistent particles. We propose application of this cutoff as a surrogate for estimating the biosolubility HMW polymers in the lysosomes of alveolar macrophages (*e.g.*, artificial lysosomal fluid).

The above screening criteria for respirability, reactivity, and biosolubility provide a framework for determining inclusion/exclusion from the HMW polymer category, as shown in Scheme 2. The screening criteria may be used for determining whether further evaluation of the new chemical substance is warranted using the tiered-testing strategy discussed later in this document.

Scheme [SEQ Scheme * ARABIC]. Framework for determining whether a chemical substance is included/excluded from the HMW polymer category.



Based on the above information, the HMW polymer category was defined to include a variety of respirable, non-reactive (*i.e.*, low toxicity), and poorly soluble HMW (*i.e.*, ≥ 10,000 Daltons)

materials, which meet the ~~above-stated~~ criteria for these parameters. HMW polymers ~~meeting these criteria are those which~~ are typically formed through various polymerization processes. ~~Chemical substances~~, included ~~are~~ branched and linear polymers, as well as co-polymers produced by random, block, graft, or other techniques. Crosslinked polymers were included in the category because crosslinking can decrease water solubility, but crosslinking was not necessary for inclusion. Therefore, the representative members of this category were refined to include polyacrylates/methacrylates, polyvinyl polymers, polyamides, and polyurethanes/polyureas. The water-dispersible forms polyacrylates/metacrylates and polyurethanes/polyureas would not present hazards for lung overload and are not included in the HMW polymer category [ADDIN EN.CITE ADDIN EN.CITE.DATA]; however, despite their exclusion from the category, they would need to be assessed for other potential hazard concerns. A summary of the structural features of these chemical substances and the chemical boundaries that were established is shown in [REF _Ref46674591 \h * MERGEFORMAT].

[EMBED ChemDraw.Document.6.0]

Figure [SEQ Figure * ARABIC]. Representative members of the HMW polymer category. Structure A, on the left, is representative of polyacrylate/methacylate members, where R is H or methyl; R' and R'' are typically alkyl or substituted alkyl, although there are currently no limits on the substituents. However, charged groups such as carboxyl groups or amine groups would tend to make the polymer dispersible in water rather than insoluble in water. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Acrylamide and methacrylamide monomers (NR'_2 replaces OR' or OR") may also be present. Structure B, on the right, is representative of polyvinyl members, where R is H or C1-C > 20. R' is typically methyl, CN, acetyloxy, Ph or Cl, although there are no current limits on R'. R' may be the same as R'' or different. This example represents a polymer containing one or two monomers, although sub-category members may comprise any number of monomers. Copolymers (e.g., including both acrylate/methacrylate and vinyl monomers) are also members of this category. Structure C, on the bottom, is representative of the polyamides group and is made of condensation polymers in which the linkages are all amide functional groups. An example is polycaprolactam, shown.

Hazard Identification

TSCA and its implementing regulations do not require upfront testing on new chemical substances. Therefore, when assessing new chemical substances, EPA generally identifies toxicological analogues to inform the potential hazards for the new chemical substances. The

systematic review of the literature was used to identify inhalation studies that assessed endpoints indicative of "overload" for potential toxicological analogues. For the purpose of defining this chemical category, overload has the same definition as identified by EPA (1996) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1996</Year><RecNum>59</RecNum><DisplayText>[37]</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797014">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Air Quality Criteria for Particulate Matter, Volume II of III</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>774, http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=219821</pages><volume>EPA/600/P-95/001bF</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]: "This is defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate which exceeds the capacity of that clearance pathway. It is a nonspecific effect noted in experimental studies, generally in rats, using many different kinds of poorly soluble particles (including TiO_2, volcanic ash, diesel exhaust particles, carbon black, and fly ash) and results in A [alveolar] region clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs and increased translocation of

particles into the interstitium." The relevant studies ~~that were identified~~ are summarized below, followed by the selection of studies on toxicological analogues that may serve as representative points of departure for assessing the potential hazard for overload ~~of some~~for new chemical substances.

Human Data

The hazard concerns discussed ~~herein~~ are limited to chronic effects in the ~~lower respiratory tract~~pulmonary (alveolar) region of rats exposed to HMW polymers. Epidemiological studies have shown increased lung burdens in workers chronically exposed to poorly soluble particles (PSPs), such as former coal miners; however, studies ~~have shown that~~with rodent models overpredict lung burdens in humans if adjustments are not made for kinetic differences in clearance and retention [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This is consistent with findings from well-conducted epidemiological studies, which have not identified an association between occupational exposure to PSPs and an increased cancer risk. Oberdorster (1995) [ADDIN EN.CITE <EndNote><Cite><Author>Oberdorster</Author><Year>1995</Year><RecNum>60</RecNum><DisplayText>[38]</DisplayText><record><rec-number>60</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595797677">60</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oberdorster, G.</author></authors></contributors><titles><title>Lung Particle Overload: Implications for Occupational Exposures to Particles</title><secondary-title>Regul Toxicol Pharmacol</secondary-title></titles><periodical><full-title>Regul Toxicol Pharmacol</full-

title></periodical><pages>123-135</pages><volume>27</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>] concluded that "evidence in humans suggest that particle-overloaded lungs, *e.g.*, in coal workers, respond with fibrosis, but no increased incidence in lung tumors has been found in this group". It has also been reported that "epidemiological data from production workers demonstrate no correlation between PSP exposure and lung cancer or other non-malignant respiratory diseases" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Though these investigations focused on PSPs, the available, yet limited data on HMW polymers provide comparable results. For example, in a recent retrospective study of Xerox workers employed between 1960 and 1982, workers exposed to toner did not show an increased risk of "all-cause" or "cause-specific" mortality. The categories evaluated included cancer (*e.g.*, lung), diabetes, cardiovascular disease, and others [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Aside from this one epidemiological study on toner exposures, the ~~available studies that evaluated~~ evaluation ~~potential hazards from~~of exposures to HMW polymers were limited to inhalation studies conducted in experimental animals as summarized below and described in further detail in Section 2 "Experimental Animal Inhalation Studies on HMW Polymers" of the Supplemental Information file.

Animal Data - Noncancer Effects

Inhalation studies performed in rats and hamsters have demonstrated effects ranging from inflammation to fibrosis after inhalation exposure to several HMW polymers including print toners comprised largely of styrene/butylmethacrylate copolymer and polyvinyl chloride dust. Several of these studies were conducted according to validated test guidelines and under good

laboratory practice (GLP) standards, and in some cases published in the peer-reviewed literature. A summary of these studies is provided below.

A series of sub-chronic and chronic studies were performed to test the inhalation effects of a water-insoluble styrene/butylmethacrylate polymer (the primary component of toner used in copy machines) of MW 70,000 in rats. In a subchronic 13-week study, rats were exposed to aerosol concentrations of toner at 0, 1, 4, 16, and 64 mg/m^3 (MMAD = 4 μm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. Dose-related increased lung weight and histological lesions (thickening of alveolar structure due to hypertrophy and hyperplasia of Type II cells) were seen in animals exposed to 16 and 64 mg/m^3. These exposure concentrations also resulted in a dose-related decrease in lung clearance, as measured by the retained quantity of the test substance in excised lungs, and increased lung particle burden [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>]. The NOAEC from this study was 4 mg/m^3.

Bellmann *et al.* (1992) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[42]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug

effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>] performed an additional 13-week study using the same test substance ~~used by~~as Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Fuhst, R.</author><author>Koch, W.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Morrow, P.</author><author>Kilpper, R.</author><author>Mackenzie, J.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Subchronic Inhalation Study of Toner in Rats</title><secondary-title>Inhalation Toxicology</secondary-title></titles><periodical><full-

title>Inhalation Toxicology</full-title></periodical><pages>341-360</pages><volume>2</volume><number>4</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.3109/08958379009145262</electronic-resource-num></record></Cite></EndNote>] and included an extended 15-month post-exposure monitoring period. Rats were exposed to aerosol concentrations of toner at 0, 10, or 40 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study authors measured retention of the toner in the lungs and lung-associated lymph nodes (LALN) by photometric determination in dissolved tissues; clearance was monitored using tracer particles, and pulmonary effects were identified from enzymatic activities and differential cell counts in bronchoalveolar lavage fluid (BALF). The study authors identified clearance half-lives of 277 and 2,845 days for the low- and high-dose exposure groups, respectively, and reported pulmonary effects, as evidenced by increases in protein and enzyme markers of tissue damage in BALF that were partially reversible at 10 mg/m^3 and not reversible at 40 mg/m^3 [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[42]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Irreversible pulmonary changes induced in rat lung by dust overload</title><secondary-title>Environ Health

Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>189-91</pages><volume>97</volume><edition>1992/07/01</edition><keywords><keyword>Animals</keyword><keyword>Bronchoalveolar Lavage Fluid/*enzymology/*pathology</keyword><keyword>Cell Count</keyword><keyword>Dust</keyword><keyword>Environmental Exposure/*adverse effects</keyword><keyword>Female</keyword><keyword>Glucuronidase/metabolism</keyword><keyword>L-Lactate Dehydrogenase/metabolism</keyword><keyword>Lung/*drug effects/enzymology</keyword><keyword>Macrophages/*drug effects/pathology/physiology</keyword><keyword>Phagocytosis/drug effects</keyword><keyword>Polymers/*adverse effects</keyword><keyword>Rats</keyword><keyword>Time Factors</keyword></keywords><dates><year>1992</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765 (Linking)</isbn><accession-num>1396457</accession-num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1396457</url></related-urls></urls><custom2>PMC1519531</custom2><electronic-resource-num>10.1289/ehp.9297189</electronic-resource-num></record></Cite></EndNote>].

Muhle *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae"

timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>] and Bellmann *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1991</Year><RecNum>3</RecNum><

DisplayText>[44]</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844572">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Kilpper, R.</author><author>MacKenzie, J. C.</author><author>Morrow, P.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, Germany.</auth-address><titles><title>Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats</title><secondary-title>Fundam Appl Toxicol</secondary-title></titles><periodical><full-title>Fundam Appl Toxicol</full-title></periodical><pages>300-13</pages><volume>17</volume><number>2</number><edition>1991/08/01</edition><keywords><keyword>Aerosols</keyword><keyword>Animals</keyword><keyword>Body Burden</keyword><keyword>Dust/adverse effects</keyword><keyword>Female</keyword><keyword>Half-Life</keyword><keyword>Lung/*metabolism</keyword><keyword>Lymph Nodes/metabolism</keyword><keyword>Male</keyword><keyword>Pulmonary Alveoli/metabolism</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Sex Factors</keyword><keyword>Silicon Dioxide/*metabolism</keyword><keyword>Titanium/*metabolism</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590 (Print)
0272-0590 (Linking)</isbn><accession-num>1662649</accession-

num><urls><related-urls><url>https://www.ncbi.nlm.nih.gov/pubmed/1662649</url></related-urls></urls><electronic-resource-num>10.1016/0272-0590(91)90220-x</electronic-resource-num></record></Cite></EndNote>] reported findings from a chronic 24-month exposure study in rats exposed to toner at aerosol concentrations of 0, 1, 4, or 16 mg/m^3 (MMAD = 4 µm; GSD = 1.5; density = 1.15 g/cm^3) for 6 hours/day, 5 days/week. The study was performed according to OECD No. 453 Combined Chronic Toxicity/Carcinogenicity Studies ~~and~~ under GLP standards. The study authors reported dose-related impaired particle clearance, elevated lung particle burden, and lung effects (fibrosis, BALF markers of tissue damage, and increased lung weight) at 4 and 16 mg/m^3, with a NOAEC of 1 mg/m^3.

Unpublished subchronic (3 months) and chronic (18 months) hamster studies of the same print toner tested by Muhle *et al.* (1990, 1991) and Bellman *et al.* (1991, 1992) [ADDIN EN.CITE ADDIN EN.CITE.DATA] showed similar effects ~~similar~~ to those in rats [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The unpublished 3-month study was hampered by disease and mortality unrelated to treatment. In the unpublished 18-month study, the hamsters were exposed to concentrations of 0, 1.5, 6, or 24 mg/m^3 for the first 5 months and then concentrations of 0, 4, 16, or 64 mg/m^3 for the remaining ~~time~~test period. At all exposure concentrations, the hamsters exhibited macrophage accumulation, interstitial inflammatory cell infiltration, and bronchiolar/alveolar hyperplasia, along with particle deposits and lymphatic hyperplasia in the LALNs. At the mid- and high-exposure concentrations, fibrosis and alveolar PMN infiltration were noted at the end of exposure and/or after the 5 month post-exposure recovery period; the highest exposure group also exhibited increased lung weight and effects on BALF parameters

(increased cell number, macrophage count, LDH, β glucuronidase, total protein, and hydroxyproline). The LOAEC for this study was in the range of 1.5 to 4 mg/m^3.

Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] performed an eight-month inhalation study in rats exposed to an aerosol of PVC powder at 0, 3.3, 8.3, or 20.2 mg/m^3 (MMAD = 1.3 μm; GSD = 2.07; density = 1.3 g/cm^3) for 5 hours/day, 5 days/week. Retention, clearance, and pulmonary effects were evaluated, as reported previously by these same authors. Using radiolabeled (^{85}Sr) polystyrene particles as tracers, these authors showed that pulmonary clearance was significantly decreased in rats after seven months of exposure (25 hours per week)

to PVC powder at concentrations ≥ 3.3 mg/m^3. Mean alveolar clearance half-times increased with exposure from 1.2-fold higher than controls to 3.2-fold higher than controls at concentrations from 3.3 to 20.2 mg/m^3. The study authors calculated half-times for alveolar clearances of 71, 122, and 184 days at exposure concentrations of 3.3, 8.3, and 20.2 mg/m^3, respectively, supporting that lung overload occurred at concentrations ≥ 3.3 mg/m^3 for this water-insoluble polymer.

Animal Data - Cancer

Chronic inhalation exposure data specifically pertaining to HMW polymers are limited to a 24-month rat study of print toner and an 18-month hamster study of print toner [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-

title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>]. No increased in the incidence of tumors ~~incidence~~ was observed in either study; however, interstitial and alveolar lung pathology has been documented in long-term inhalation studies on these polymers. See section on "Animal Data - Noncancer Effects" above.

Supporting Information

An *in vitro* study was identified and reviewed that may be relevant for determining the reactivity/non-reactivity of HMW polymers that do not meet the initial FG and/or FGEW screening criteria.

Wiemann et al. (2016) [ADDIN EN.CITE ADDIN EN.CITE.DATA] developed an *in vitro* assay to test nanoparticles for predicting biologically active ~~toxicity~~ from passive (*i.e.*, overload condition) toxicity. The assay ~~uses~~ used rat NR8383 alveolar macrophages in cell culture

medium incubated with test material ~~in cell culture medium, and~~to assesses toxicity *via* measurement of LDH, glucuronidase, and tumor necrosis factor α (TNFα) (after 16 hours exposure), and hydrogen peroxide (after 1.5 hours) ~~in the cell culture supernatant~~. The authors tested 18 inorganic nanomaterials using the assay, as well as corundum as a negative control and quartz DQ12 as a positive control. The size and shape of the test substances ranged from 9 nm to <30 µm and from 15 m^2/g to 200 m^2/g. Based on data from short term inhalation studies, each test material was categorized as either active (NOAEC <10 mg/m^3 for adverse inflammatory action in a 5-day inhalation study) or passive (*i.e.*, inducing nonspecific cell overload). The *in vitro* assay used a particle surface area-based threshold of <6000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in µg/mL) to determine the biological relevance of the lowest observed significant *in vitro* effects ~~threshold for active toxicity was a surface-area/volume concentration of 6,000 mm^2/mL (calculated as particle or agglomerate Brunauer Teller and Emmett [BET] surface area × mass concentration in µg/mL)~~ in at least two of the four measured parameters ~~measured in supernatant~~. The results for the nanomaterials ~~tested~~ showed good ~~correspondence~~ correlation between the *in vitro* and *in vivo* parameters (assay accuracy 95%), suggesting that, the assay could be useful in distinguishing specific ("active") toxicity from nonspecific ("passive" or overload) effects on alveolar macrophages. Although only nanoparticles were tested by these authors, this assay may be useful for screening out HMW polymers for inclusion/exclusion in the category, *e.g.*, those identified as "active" would be inconsistent with the low-concern level and inclusion in the category, whereas those identified as "passive" appear to be consistent with inclusion. Additionally, this assay could be useful for screening polymers with specific toxicities (*i.e.*, excluded from overload category) prior to *in vivo* testing of "overload" for passive polymers.

Quantitative Points of Departure (PODs)

A single epidemiological study of inhaled HMW polymers was identified - the retrospective study of Xerox workers [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This study did not report exposure concentrations associated with the evaluated health outcomes and is therefore not useful for determining quantitative PODs for pulmonary effects of HMW polymers.

A summary of animal studies documenting pulmonary effects after exposure to HMW polymers and the PODs identified from them is provided in [REF _Ref46678612 \h * MERGEFORMAT]. The PODs presented in the table include those from studies meeting the following criteria:

- Exposure was *in vivo via* inhalation (*in vitro*, intratracheal instillation studies were not included);
- Exposure continued for at least 13 weeks; and
- Critical study information was reported, including exposure concentrations, exposure regimen~~frequency~~, and aerodynamic particle size (MMAD ~~and~~, GSD, and density).

Each study was evaluated to determine whether the data were amenable for BMD modeling.

~~For the polyacrylates and methacrylates subcategory, s~~Several subchronic studies, for the polyacrylates and methacrylates subcategory that met the initial POD selection criteria, are included in [REF _Ref46678612 \h * MERGEFORMAT] ~~that met the initial POD selection criteria~~; however, BMD modeling was not performed on these studies because chronic studies

were available and ~~deemed~~ considered more relevant for ~~the~~ hazard assessment with identifying health protective PODs. Two chronic studies met the POD selection criteria: the published 24-month rat study of 9000 type toner and the unpublished 18-month hamster study of the same toner [ADDIN EN.CITE ADDIN EN.CITE.DATA]. BMD modeling was performed ~~for the data in~~on the rat study performed by Muhle *et al.* (1991) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1991</Year><RecNum>16</RecNum><DisplayText>[43]</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846537">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Dasenbrock, C.</author><author>Ernst, H.</author><author>Kilpper, R.</author><author>Mackenzie, J. C.</author><author>Morrow, P.</author><author>Mohr, U.</author><author>Takenaka, S.</author><author>Mermelstein, R.</author></authors></contributors><auth-address>Xerox Corp,Joseph C Wilson Ctr Technol,Corp Environm Hlth,Webster,Ny 14580
Univ Rochester,Rochester,Ny 14642</auth-address><titles><title>Pulmonary Response to Toner Upon Chronic Inhalation Exposure in Rats</title><secondary-title>Fundamental and Applied Toxicology</secondary-title><alt-title>Fund Appl Toxicol</alt-title></titles><periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></periodical><alt-periodical><full-title>Fundamental and Applied Toxicology</full-title><abbr-1>Fund Appl Toxicol</abbr-1></alt-periodical><pages>280-299</pages><volume>17</volume><number>2</number><keywords><keyword>bronchoalveolar lavage fluid</keyword><keyword>diesel

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exhaust</keyword><keyword>toxicity</keyword><keyword>clearance</keyword></keywords><dates><year>1991</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>0272-0590</isbn><accession-num>WOS:A1991FZ99700006</accession-num><urls><related-urls><url><Go to ISI>://WOS:A1991FZ99700006</url></related-urls></urls><electronic-resource-num>Doi 10.1016/0272-0590(91)90219-T</electronic-resource-num><language>English</language></record></Cite></EndNote>], ~~as~~because it used a longer exposure duration, was published in a peer-reviewed journal, and did not change exposure concentrations during the study. ~~, whereas, in t~~The hamster study, modified the exposure concentrations ~~were modified~~ after the first five months. ~~Among t~~The endpoints affected at the LOAEC in ~~that~~ the rat study (macrophages, PMN, and lymphocytes in BAL; incidence of pulmonary fibrosis), only the incidence of fibrosis ~~incidence~~ could be modeled, as the BALF parameters were reported without measures of variability (*i.e.*, standard deviation or standard error). The incidences of lung fibrosis (summed across severity categories) were subjected to BMD modeling, as described in Section 3 "Benchmark Dose (BMD) Modeling Outputs" of the Supplemental Information file. The BMCL from the best-fitting model was 2.5 mg/m^3, as shown in [REF _Ref46678612 \h * MERGEFORMAT].

Only a single study was available for the polyvinyl subcategory; however, BMD modeling on the alveolar clearance for the tracer was not possible because of the absence of reported measures of variability ([REF _Ref46678612 \h * MERGEFORMAT]).

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyacrylates and Methacrylates Sub-category							
9000 Toner (styrene/butylmethacrylate random copolymer)	SPF F344 rats, male and female (288/group); 24 months (6 hr/d, 5 d/wk), 2 months recovery	0, 1, 4, or 16	1	4	2.5 (fibrosis)	Significantly decreased macrophages and increased PMN and lymphocytes in BAL; significantly increased incidence of minimal to mild pulmonary fibrosis	[ADDIN EN.CITE ADDIN EN.CITE.DATA]

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
9000 Toner (styrene/butylmet	Syrian Golden Han:AURA Hamster, male and female,	0, 1.5, 6, or 24 (months 1-5); 0,	ND	1.5-4	Not derived; variable	Significantly increased incidences of bronchiolar/alveolar hyperplasia (males); accumulation of particle-laden macrophages in lungs; interstitial	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>30</RecNum><DisplayText>[51]</DisplayText><record><rec-number>30</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849152">30</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Toner A (styrene/butylmethacrylate random	F344/CrlBR rat, female, (58-66/group); 3 months (6 hr/d, 5 d/wk); up to 6	0, 4, 16, or 64	ND	4	Not derived	Significantly increased incidence slight to moderate accumulation of particle-laden macrophages in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>28</RecNum><DisplayText>[45]</DisplayText><record><rec-number>28</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848985">28</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1992</Year><RecNum>4</RecNum><DisplayText>[42]</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590844601">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author>

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>14</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590846288">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Toner B (styrene/ butadiene random copolymer)	F344 rat, female (50 rats/group for main study) up to 6 mo.	0, 1, 4, 16, or 64	4	16	Not derived	Significantly increased incidence very slight to slight focal/multifocal interstitial inflammatory cell infiltration in lungs	[ADDIN EN.CITE <EndNote><Cite><Author>Institute</Author><Year>1991</Year><RecNum>29</RecNum><DisplayText>[52]</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590849070">29</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>Fraunhofer Institute</a

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Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
Polyvinyls Sub-Category							

Table [SEQ Table * ARABIC]. Available PODs for inhalation studies on HMW Polymers.

Test material	Strain, Species, Sex, Exposure frequency and duration, Recovery	Exposure Concentrations (mg/m^3)	NOAEC (mg/m^3)	LOAEC (mg/m^3)	BMCL (mg/m^3)	Lung Effects at LOAEC	Reference
							[ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Be

Study Selection for establishing sub-category points of departure (PODs)

In rats, the key events in the development of lung tumors ~~in rats~~ in response to inhalation of inorganic PSPs of low toxicity (as outlined by ECETOC 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>], Bevan *et al.*, 2018 [ADDIN EN.CITE ADDIN EN.CITE.DATA], Driscoll and Borm, 2020 [ADDIN EN.CITE <EndNote><Cite><Author>Driscoll</Author><Year>2020</Year><RecNum>40</RecNum><DisplayText>[54]</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595775199">40</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Driscoll, K. E.</author><author>Borm, P. J. A.</author></authors></contributors><auth-address>Healthcare Innovation Partners, Princeton, NJ, USA.
Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA.
Nanoconsult BV, Meerssen, The Netherlands.
Dusseldorf University, Dusseldorf, Germany.</auth-address><titles><title>Expert workshop on the hazards and risks of poorly soluble low toxicity particles</title><secondary-title>Inhal Toxicol</secondary-title><alt-title>Inhalation toxicology</alt-title></titles><alt-periodical><full-title>Inhalation Toxicology</full-title></alt-periodical><pages>53-62</pages><volume>32</volume><number>2</number><edition>2020/03/10</edition><keywords><keyword>*pslt</keyword><keyword>*hazard</keyword><keyword>*inhalation</keyword><keyword>*lung cancer</keyword><keyword>*lung particle overload</keyword><keyword>*particles</keyword><keyword>*risk</keyword></keywords><dates><year>2020</year><pub-dates><date>Feb</date></pub-dates></dates><isbn>0895-8378</isbn><accession-num>32149535</accession-num><urls></urls><electronic-resource-num>10.1080/08958378.2020.1735581</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]) are: (1) impaired pulmonary clearance, (2) persistent neutrophilic inflammation, (3) increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and (4) proliferation of cells initiated by secondary genotoxicity (from ROS, RNS, and/or inflammation) and tumor formation.

Though the key events for lung overload from HMW polymers have not been thoroughly studied, the available data ~~as reviewed herein~~ suggests that HMW polymers may lead to lung overload in the rat through similar key events. It should be noted that cytotoxicity to macrophages by a poorly soluble HMW polymer or components present in the polymer may negatively impact clearance *via* alveolar macrophages~~, thereby leading to tumor formation in humans~~. However, substances with these properties (*i.e.*, cytotoxicity) would not be included within the boundaries for the HMW polymers category.

Of the studies listed in [REF _Ref46678612 \h * MERGEFORMAT], PODs of 2.5 mg/m^3 and 3.3 mg/m^3 were identified for the polyacrylates/ methacrylates sub-category and the polyvinyls sub-category, respectively. The 24-month study on the 9000 Toner with a $BMCL_{10}$ of 2.5 mg/m^3 for pulmonary fibrosis was selected as a principle study for polyacrylates/methacrylates because it was the longest duration study ~~on this sub-category of materials~~ and was conducted in the most susceptible species for lung overload (*i.e.*, the rat). Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-

title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] was selected as a principle study for identifying a LOAEC of 3.3 mg/m^3 for the polyvinyls sub-category because it was based on decreased alveolar clearance, which is the first key event in the proposed adverse outcome pathway for lung overload from PSPs in the rat [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These study PODs represent potential starting points for evaluating new chemical substances that fit within one of the HMW polymer sub-categories. EPA may determine that either of these PODs is an acceptable toxicological analogue for chemistries that do not fit within the sub-categories but are anticipated to have ~~comparable or greater~~a potential for ~~causing~~ lung overload in the rat than the new chemical substance under evaluation. For example, EPA generally uses the POD of 3.3 mg/m^3 for quantifying the potential risks of HMW polymers, even for chemistries that would not fall within the polyvinyls sub-category, based on the properties of the new chemical substance ~~compared to the PVC powder~~. Notwithstanding this, we recognize that data on a new chemical substance or an alternative analogue would take precedence over using one of these analogues as the default POD, if EPA concludes there are no study limitations on the new chemical substance or alternative analogue that would preclude the use of those data.

Due to the limited data on HMW polymers, available knowledge about inorganic PSPs was used to make inferences about HMW polymers. Compared to systemic effects, lung overload responses to inorganic PSPs show large variations in susceptibility between and among

mammalian species, with the rat being the only species to develop lung tumors [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. This species-specific response has been explained by species differences in the accumulation of insoluble and respirable particles in the lungs, although cytotoxicity is also an issue with some inorganic PSPs (*e.g.*, crystalline silica). ~~For example,~~ hHumans are at least six times more resistant to attaining lung overload conditions than rats for the following reasons: human alveolar macrophages (AMs) are larger (*i.e.*, average volume = 4,990 μm^3) than rat AMs (*i.e.*, average volume = 1,166 μm^3); humans have a greater number of AMs (*i.e.*, average = 7.0×10^9) than rats (*i.e.*, average = 2.6×10^7); and human AMs patrol a smaller surface area (*i.e.*, average = 22,000 μm^2/AM) than

rat AMs (*i.e.*, average = 140,000 μm^2/AM) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Further, the site of retention for poorly soluble particles differs between rats and humans. Nikula *et al*. (2001) [ADDIN EN.CITE <EndNote><Cite><Author>Nikula</Author><Year>2001</Year><RecNum>62</RecNum><DisplayText>[56]</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803440">62</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nikula, K. J.</author><author>Vallyathan, V.</author><author>Green, F. H.</author><author>Hahn, F. F.</author></authors></contributors><auth-address>Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87185, USA.</auth-address><titles><title>Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs</title><secondary-title>Environ Health Perspect</secondary-title><alt-title>Environmental health perspectives</alt-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>311-8</pages><volume>109</volume><number>4</number><edition>2001/05/04</edition><keywords><keyword>Adult</keyword><keyword>Air Pollutants/*pharmacokinetics</keyword><keyword>Animals</keyword><keyword>Coal</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Dust</keyword><keyword>Humans</keyword><keyword>*Inhalation Exposure</keyword><keyword>Lung/*chemistry</keyword><keyword>Macrophages, Alveolar</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>*Mining</keyword><keyword>*Occupational

Exposure</keyword><keyword>Particle Size</keyword><keyword>Rats</keyword><keyword>Rats, Inbred F344</keyword><keyword>Vehicle Emissions/*analysis</keyword></keywords><dates><year>2001</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>0091-6765 (Print)
0091-6765</isbn><accession-num>11335177</accession-num><urls></urls><custom2>PMC1240269</custom2><electronic-resource-num>10.1289/ehp.01109311</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] showed that "the relative amounts of intraluminal and interstitial particle load differ markedly between rats and humans with particles being found predominantly in the interstitium in man and intra-luminarly in rats." In rats, accumulation of particulate matter in the intraluminal space leads to adverse "alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses" [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-

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As noted previously, EPA generally uses the polyvinyls sub-category analogue (*i.e.*, PVC powder) POD of 3.3 mg/m^3 for evaluating new chemical substances that may present a lung overload hazard when the chemical properties are comparable ~~between the new chemical substance and the PVC powder~~. The polyvinyls sub-category POD is then subject to the established EPA dosimetry adjustment. Each of these approaches is discussed below. These dosimetric adjustments may also be applied to the polyacrylates/methacrylates sub-category analogue (9000 Toner), as well as to data on new chemical substances or other potential analogues that fit within the chemical boundaries for this category.

As shown in [REF _Ref519678474 \h * MERGEFORMAT], the RDDRs for the PVC powder ranged from 0.501 in the pulmonary region (PU) ~~up~~ to 2.248 in the tracheobronchial (TB) region. Since the effects occurred in the PU region, the PU (surface area: 0.34 m^2 [rat]; 54 m^2 [human]) RDDR was used for deriving a POD_{HEC}, as follows:

$$POD_{HEC} = POD \times RDDR_{PU}$$

or

$$POD_{HEC} = 3.3 \text{ mg/m}^3 \times 0.5 = 1.65 \text{ mg/m}^3$$

Table [SEQ Table * ARABIC]. Depositional fractions and RDDRs for rats and humans.[a]

SPECIES	Extrathoracic (ET)		Tracheobronchial (TB)		Pulmonary (PU)		Thoracic (TB + PU)		Total Respiratory Tract (RT)	
	Surface Area (cm^2)	Depositional Fraction	Surface Area (cm^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction	Surface Area (m^2)	Depositional Fraction
Rat	15	0.33	22.5	0.068	0.34	0.061	0.342	0.129	0.344	0.459
Human	200	0.24	3200	0.059	54	0.267	54.32	0.125	54.34	0.566
RDD	0.075	1.373	0.007	1.15	0.006	0.229	0.006	1.028	0.006	0.811
RDDR	0.252		2.248		0.501		0.863		1.763	

[a] Inputted values included: MMAD = 1.30; GSD = 2.07; density = 1.3 g/cm^3.

In comparison, the MPPD model was used to conduct simulations to predict retained mass burden in the PU region of female F344 rats exposed in the Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. The geometry model in the MPPD software for the Sprague-Dawley rat was used, but with the Agency default body weight (BW) of 229 grams for female F-344 rats in a chronic study [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD software internally scales ventilation parameters and respiratory volumes based on BW, so this resulted in tidal volume (V_T) of 1.54, a breathing frequency of 166 bpm, functional residual capacity (FRC) of 3.01 mL, and an upper respiratory tract (URT) volume of 0.34 mL. The 229 g rat PU surface area is predicted to be 1997 cm^2. The particle MMAD, GSD of the particle size distribution, and its density were: 1.3 μm, 2.07, and 1.3 g/cm^3, respectively. The regimen and duration of the nose-only exposure in the Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust

overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study was 5 h/d and 5 d/w for 8 months and was used in the simulation. We note that there were discrepancies in the reported duration of exposure of 7 months versus 8 months in Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. However, the Bellmann *et al.*

(1986) [ADDIN EN.CITE <EndNote><Cite><Author>Bellmann</Author><Year>1986</Year><RecNum>77</RecNum><DisplayText>[57]</DisplayText><record><rec-number>77</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595887108">77</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bellmann, B.</author><author>Muhle, H.</author><author>Creutzenberg, O.</author></authors></contributors><titles><title>The Effect of a "Nuisance" Dust Inhalation of Lung Clearance</title><secondary-title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference</secondary-title></titles><periodical><full-title>Aerosols, Formation and Reactivity, Proceedings of the Second International Aerosol Conference</full-title></periodical><pages>209-211</pages><dates><year>1986</year></dates><urls></urls></record></Cite></EndNote>] abstract consistently reported an 8-month exposure duration; therefore, a duration of 8-months was used.

Using the above experimental conditions, the predicted retained mass in the PU region of F344 rats, shown in [REF _Ref46766078 \h * MERGEFORMAT], demonstrated the goodness of fit of the MPPD model to the experimental data reported by Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. For example, Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates>

<urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] reported a retained PU mass of 0.56 mg in rats exposed to 3.3 mg/m^3; the MPPD model predicted a retained PU mass of 0.63 mg at this exposure concentration. Additional simulations were conducted using the same three exposure concentration as Muhle *et al*. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>], but the key input parameters for MMAD, GSD, and density were varied and bounded. Details on the additional simulations are provided under "Section 4 MPPD Modeling Outputs" of the Supporting Information file. These additional simulations reinforce that prediction of overload kinetics is specific to the particle physicochemical properties (size, distribution, and density) and experimental regimen. Such

simulation demonstrations can be useful to defining whether a given particle and exposure conditions achieve overload.

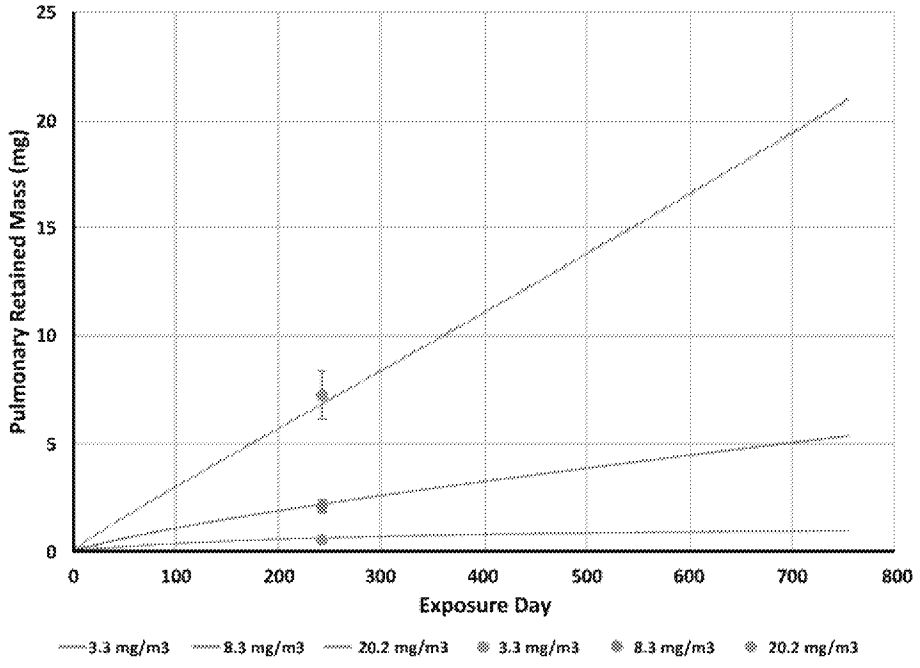

Figure [SEQ Figure * ARABIC]. MPPD predictions for retained PU mass in F344 rats under the exposure conditions for the Muhle et al. (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar,

M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>] study. Simulations were performed to characterize the 8-month study with a particle MMAD size of 1.3 μm, a GSD of 2.07, and a density of 1.3 g/cm^3 for three concentrations (3.3, 8.3, and 20.2 mg/m^3). Experimental data for PU burdens are shown as solid circles with standard deviation and the predictions as solid lines for different concentrations.

For extrapolation of the predicted rat retained PU mass to an HEC, human simulations were conducted for adult males with a V_T of 0.992 L and a breathing frequency of 21 bpm, or with 1.364 L and 33 bpm. These ventilatory values are from the ICRP (1994) [ADDIN EN.CITE <EndNote><Cite><Author>ICRP</Author><Year>1994</Year><RecNum>26</RecNum><DisplayText>[24]</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590848620">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>ICRP</author></authors></contributors><titles><title>Human respiratory tract model for radiological protection. A report of a Task Group of the International Commission on Radiological Protection</title><secondary-title>Ann

ICRP</secondary-title><alt-title>Annals of the ICRP</alt-title></titles><periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></periodical><alt-periodical><full-title>Ann ICRP</full-title><abbr-1>Annals of the ICRP</abbr-1></alt-periodical><pages>1-482</pages><volume>24</volume><number>1-3</number><edition>1994/01/01</edition><keywords><keyword>Humans</keyword><keyword>International Cooperation</keyword><keyword>*Models, Theoretical</keyword><keyword>Neoplasms, Radiation-Induced/*etiology/pathology/physiopathology</keyword><keyword>Radiation Dosage</keyword><keyword>*Radiation Monitoring</keyword><keyword>*Radiation Protection</keyword><keyword>Radioactive Pollutants</keyword><keyword>Respiratory System/pathology/physiopathology/*radiation effects</keyword><keyword>Respiratory Tract Neoplasms/*etiology/pathology/physiopathology</keyword></keywords><dates><year>1994</year></dates><isbn>0146-6453 (Print)
0146-6453</isbn><accession-num>7726471</accession-num><urls><related-urls><url>https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3</url></related-urls></urls><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and represent ventilation associated with activity levels of either light exercise or heavy exercise for adult males. It should be noted that this combination of V_T and bpm for the light exercise ventilation input parameters are equivalent to the default minute ventilation value (V_E) found in [REF _Ref46666189 \h * MERGEFORMAT] of 1.25 m^3/hr. An occupational exposure duration of 40 years was simulated for the human predictions of retained mass in the PU region.

The dose metric used to operationally derive the HEC is the PU retained mass (mg) normalized to the PU surface area (SA) in cm^2 according to the established US EPA methods [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><DisplayText>[18]</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>]. The MPPD model estimates a human pulmonary surface area of 66.3 m^2 for an 80 kg adult male. As shown in [REF _Ref46767442 \h * MERGEFORMAT], simulations were performed iteratively to arrive at an HEC that achieved the same internal dose metric (PU mass / PU SA) in humans as was achieved in rats under the experimental conditions reported by Muhle *et al.* (1990) [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key

app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle, H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>]. As was shown in [REF _Ref46766078 \h * MERGEFORMAT], the predicted retained mass in the PU region corresponds well with the observed experimental data. The last two rows of [REF _Ref46767442 \h * MERGEFORMAT] demonstrate the difference in HEC value due to variation in ventilatory parameters associated with either light or heavy activity.

Table [SEQ Table * ARABIC]. MPPD predictions and HEC calculations for Muhle *et al*. (1990) study of F344 rats exposed to PVC with a particle MMAD of 1.3 μm, GSD of 2.07 and density of 1.3 gm / cm^3.

Exposure Concentration (mg/m^3)	**3.3**	**8.3**	**20.2**
Experimental Rat Retained PU Mass (mg)	0.56±0.16	2.09±0.29	7.24±1.10
Predicted Rat Retained PU Mass (mg)	0.63	2.21	6.88
Predicted Rat Retained PU Mass / PU SA (mg/m^2)	2.8	10.5	36.3
Light Activity 40-Year HEC (mg/m^3)	0.33	1.23	4.25

Heavy Activity 40-Year HEC (mg/m^3)	0.14	0.53	1.84

HEC = human equivalent concentration that results in the same inhaled dose metric (retained PU mass / PU SA) as predicted for the rat. The human ventilatory parameters of the light and heavy activity levels for simulation of 40-year occupational scenario are described in the text.

Category benchmark margin of exposure (MOE)

EPA currently applies a benchmark MOE ~~composite UF~~ of 1,000 ~~as the benchmark MOE for~~to the PVC powder POD of 3.3 mg/m^3. The composite UF consists of default values of 10 for UF_H, UF_A, and UF_L. This default approach was initially established as a conservative means of evaluating new chemistries on HMW polymers, which were anticipated to present a hazard concern for lung overload. ~~However, s~~Several refinements to these values may be made~~, including reducing~~ ~~the~~ The TK and TD components of the UF_A value and reducing the UF_L. Dosimetric adjustments using the RDDR model or the MPPD model, as discussed above, may be applied to calculate a POD_{HEC}, thereby reducing the TK component of the UF_A to 1. Since lung overload is a chronic effect that is manifested primarily based on the retained dose in the PU region, the RDDR model is not necessarily the most appropriate for deriving a POD_{HEC}, given that deposition is a more relevant metric for short-term effects/exposures. However, the RDDR model was used to provide comparative estimates of the MOE to the ~~other approaches versus the~~ respective benchmark MOE, given that the RDDR ~~approach~~ model is recommended in EPA guidance as the default for quantifying POD_{HEC}s for particles. For the TD component, a reduced value of 1 may be applied based on the proposal from the ILSI Workshop Consensus Report on rat lung response to particle overload, which stated: "For both neoplastic and fibrogenic endpoints in the rat, associated with PSP exposures, the work group proposed that the TD component of the interspecies UF be reduced from a factor of 3 to 1, given that chronic active

inflammation in the rat appears to be a more sensitive response than in other species, including humans" [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The UF_L may be reduced from 10 to 1 for the PVC powder analogue POD because default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathway~~this dose represented the point at which retardation of alveolar clearance started, based on the retained mass of about 0.5 mg/lung~~. This approach is consistent with EPA (2002) [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>], which states that the UF_L "may be altered, depending on the magnitude and nature of the response at the LOAEL". ~~Further, the default application of this UF is for apical endpoints, rather than initial key events in an adverse outcome pathway~~. Based on the foregoing considerations, the following values are proposed for deriving the benchmark MOE for HMW

polymers, which are generally applicable regardless of whether the POD is derived from an analogue or a new chemical substance.

UF_H = 10: The default value of 10 should be applied, unless there are human data showing which age groups or time periods are the most sensitive to lung overload. This approach is consistent with EPA's guidance for reducing the default UF_H [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>].

UF_A = 3 or 1: A reduced value of 1 should be applied for the TD component based on the ~~proposal~~ consideration documented by Olin (2000). In addition, if the data are amenable for deriving a POD_{HEC}, the dosimetric adjustment for the TK component further supports reducing

this UF [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>46</RecNum><DisplayText>[14, 18]</DisplayText><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788591">46</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>1994</Year><RecNum>47</RecNum><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595788909">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina</full-

title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EP/600/9-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>].

UF_L = 10 or 1: A value of 1 should be applied when the POD is based on a study NOAEC or when BMD modeling is applied to derive a BMCL, per EPA guidance [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>49</RecNum><DisplayText>[15]</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595789576">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Benchmark Dose Technical Guidance</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460</full-title></periodical><pages>99, https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>]. The default value of 10 should be applied when the POD is based on a study LOAEC; however, a reduced value may be used, when ~~for example,~~ the LOAEC is based on key event 1 from the proposed adverse outcome pathway for PSPs. Reductions in the UF_L based on other key

events should be made on a case-by-case basis and supported by discussion of the key event within the context of an established AOP.

The default and dosimetrically adjusted PODs and benchmark MOEs derived on new chemical substance risk assessments are used to inform risk management options for addressing potential risks. Therefore, values derived using dosimetric adjustments may allow for refined estimates ~~For example, the default POD of 3.3 mg/m^3 and benchmark MOE of 1,000 result in an MOE of 2.0E-01 that would require~~for determining the appropriate engineering controls and/or ~~a respirator with an applied protection factor (APF) of 1,000~~personal protective equipment. ~~In comparison, when dosimetric adjustments are applied using the MPPD modeling outputs, the POD$_{\text{HEC-light activity}}$ of 0.33 mg/m^3 and refined benchmark MOE of 10 result in an MOE 1.7, which indicates that engineering controls and/or a respirator with an APF of 10 would be required.~~

Uncertainties and Limitations

The available toxicological studies for HMW polymers lack data on materials with molecular weights < 70,000 Daltons [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>63</RecNum><DisplayText>[59]</DisplayText><record><rec-number>63</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595803909">63</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>High Molecular Weight Polymers in the New Chemicals Program</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania

Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/high-molecular-weight-polymers-new</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. In addition, the following uncertainties and study limitations were noted, that if known, may serve to refine the boundaries for this category:

- Physicochemical properties can influence deposition of inhaled particles (*e.g.*, particle size, distribution, density, and hygroscopicity) while ~~and biopersistence and bioreactivity (*e.g.*,~~ solubility, surface chemistry, and composition~~).~~ determine biopersistence and bioreactivity and thereby impact clearance and retention. However, the available studies of test materials in this category are generally missing information on these properties, with the exception of particle size.
- Information on molecular weight was not reported for test materials used in the studies of the PVC powder [ADDIN EN.CITE <EndNote><Cite><Author>Muhle</Author><Year>1990</Year><RecNum>13</RecNum><DisplayText>[48]</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845894">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muhle,

H.</author><author>Bellmann, B.</author><author>Creutzenberg, O.</author><author>Heinrich, U.</author><author>Ketkar, M.</author><author>Mermelstein, R.</author></authors></contributors><titles><title>Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies</title><secondary-title>Journal of Aerosol Science</secondary-title></titles><periodical><full-title>Journal of Aerosol Science</full-title></periodical><pages>374-377</pages><volume>21</volume><number>3</number><dates><year>1990</year></dates><urls></urls><electronic-resource-num>https://doi.org/10.1016/0021-8502(90)90062-3</electronic-resource-num></record></Cite></EndNote>].

- The test materials administered in the 9000 toner studies [ADDIN EN.CITE ADDIN EN.CITE.DATA] included colorant materials (predominantly carbon black) at up to 10%, and the influence of these colorants on the observed effects is unknown.
- The PODs summarized in [REF _Ref46678612 \h * MERGEFORMAT] for the HMW polymers were reported on a mass/volume basis. However, there is evidence that number of particles, particle volume, and/or volume of particles retained in the lung can influence the threshold at which lung overload conditions occur [ADDIN EN.CITE ADDIN EN.CITE.DATA]. ~~Thus, particle density may be an important consideration in identifying a POD; however, the appropriate density metric and how density should be incorporated remain uncertain.~~ Data emerging on nanomaterials and ambient ultrafine particles also increasingly suggest surface area may determine toxicity. Thus, different internal dose metrics should be explored. This can be done readily with dosimetry models as described.

- Particle morphology, reactive groups, and cytotoxicity can impede clearance pathways and induce other mechanisms of toxicity in rodents and humans. These factors include covalent binding to lung tissues, toxicity to clearance macrophages/cilia and particles lodging in pulmonary tissues which may not be considered in aerodynamic models. An *in vitro* macrophage clearance assay utilizing human or primate cells and rat cells would be potentially useful information to determine whether new chemistries fall within or outside the boundaries for this category.

An additional, important consideration pertains to the uncertainty ~~associated~~ association ~~with~~ of the human relevance of lung tumors observed in rats exposed to PSPs. ~~The available data clearly demonstrate that the rat is a sensitive model for non-neoplastic pulmonary effects following repeated exposure to PSPs, which have also been shown to occur in occupational cohorts (e.g., coal miners).~~ The rat ~~also~~ appears to be unique among species with regard to carcinogenesis in the lung due to particle overload. Lung tumors following chronic exposure to PSPs have been reported in rats, but have not been reported in mice, hamster, non-human primates, or humans [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-

Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]. Despite the uncertainty in the carcinogenicity of inhaled PSPs, the rat model remains a useful model for lung overload because it is a sensitive model for inflammatory response to PSPs, and ~~because~~ protecting against inflammation and proliferation may also protect against tumor formation [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Tiered-testing Strategy

The POD and benchmark MOE derived herein provide an analogue/read-across approach for assessing new chemical substances that fit within the chemical category boundaries for HMW polymers~~, also defined herein~~. As with any analogue read-across, assessors must carefully consider the comparability of the new chemical substance to the analogue or another acceptable toxicological analogue.; ~~this~~ This framework provides specific criteria for evaluating whether a new chemical substance "fits" into the HMW polymer category (*i.e.*, not chemically reactive, insoluble in water, not expected to be directly cytotoxic, not expected to release toxic degradates). Additionally, we demonstrate the utility of dosimetry modeling to inform evaluation or experimental design.

~~When~~ If information is not available to evaluate whether the new chemical substance fits within the category boundaries and ~~the analogue is appropriate for~~no acceptable toxicological analogue is available for use in a risk assessment, testing should be performed to aid with refining the evaluation of new chemistries that ~~are anticipated to~~may present a potential lung overload hazard. A tiered-testing strategy that is consistent with the reduced vertebrate testing requirements under the amended TSCA is provided. Though this strategy does not completely exclude vertebrate testing, it maximizes the use of NAMs for determining whether vertebrate testing should be considered. This strategy incorporates *in chemico* and/or *in vitro* characterization of the chemical substance in Tier I (*e.g.*, particle size distribution, density, reactivity, and biosolubility measurements). For substances that have particles in the respirable range, are non-reactive, and are not biosoluble, computational screening is included under Tier II to determine whether the HMW polymer is estimated to exceed the clearance t½ in the rat or demonstrate overload under anticipated use conditions. If the HMW polymer is expected to exceed the clearance t½ in the rat, then risk management options or strategic *in vivo* testing is proposed as a final option under Tier III.

Commented [ST5]: Comment from Ann: "Can we add a statement that if the PMN submitter prefers not to use the EPA "analog", they may generate the data on their specific HMW polymer?"

TS: Does the correction to the text make this clear? Can't believe I overlooked that typo so many times.

Commented [ST6]: Comment from Stephanie: "There is no density characterization in Tier I. Do we want to mention it here?"

TS: If this is not a routine measure for HMW polymers, we should add it to the testing since it will be needed to do the model simulations.

Tier I

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- **Particle Size Distribution** or Aerosolized Droplet Size of particle in use (*i.e.*, cascade impactor, laser methods, *e.g.*, OECD TG 110 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>1981</Year><RecNum>64</RecNum><DisplayText>[61]</DisplayText><record><rec-number>64</rec-number><foreign-keys><key app="EN" db-

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ilibrary.org/environment/test-no-110-particle-size-distribution-fibre-length-and-diameter-
distributions_9789264069688-
en</pages><volume>110</volume><dates><year>1981</year></dates><urls></urls></r
ecord></Cite></EndNote>], OPPTS 830.7520 [ADDIN EN.CITE
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<title>Particle Size, Fiber Length, and Diameter Distribution</title><secondary-
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1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-
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Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC

20460</full-title></periodical><pages>13, https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-830-product-properties-test-guidelines</pages><volume>EPA 712-C-96-037</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>]) of the new chemical substance during specific use(s) (*i.e.*, depending on the intended or known uses of the chemical substances, particle size distribution may need to be tested under more than one use scenario)

- If the % of respirable particles (*i.e.*, ≤ 10 μm) is less than 1 wt% under the conditions of use, or following transport, stop at Tier I.
- If the % of respirable particles (*i.e.*, ≤ 10 μm) is greater than 1 wt% under the conditions of use, or if respirable particles are anticipated or shown to be generated following transport (> 1%), then proceed with reactivity testing, if needed, or biosolubility testing.

- **Reactivity**

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  - If the HMW polymer is a potential concern for reactivity, based on ~~function or~~ other information (*e.g.*, does not meet the E1 FG/FGEW criteria), reactivity should be assessed using an *in vitro* method, preferably discussed with EPA in a pre-notice consultation meeting and prior to study initiation. The assay developed by Wiemann *et al.* (2013) [ADDIN EN.CITE ADDIN EN.CITE.DATA] provides a potential option; however, there are caveats with its use, such as not being validated and uncertainty with whether the test method could be used with HMW polymers, underscoring the recommendation to consult with EPA prior to testing using this method or other test methods.

- If substance is "reactive" (*e.g.*, does not met the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, it would be excluded from the HMW polymer category. If evidence indicates the substance is "non-reactive" (*e.g.*, it does meet the E1 FG/FGEW criteria) or based on data from the identified assay or any other appropriate assay, then proceed to biosolubility testing.

- **Biosolubility Testing**

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  - Solubility in Gamble's solution (*e.g.*, ECETOC, 2013 [ADDIN EN.CITE <EndNote><Cite><Author>ECETOC</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>[32]</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1590845309">9</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>ECETOC</author></authors></contributors><titles><title>Poorly Soluble Particles / Lung Overload</title></titles><pages>130, http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</pages><number>Technical Report No. 122</number><dates><year>2013</year><pub-dates><date>December 2013</date></pub-dates></dates><pub-location>Brussels, Belguim</pub-location><publisher>European Centre for Ecotoxicology and Toxicology of

Chemicals</publisher><work-type>Technical Report</work-type><urls><related-urls><url>http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-122-Poorly-Soluble-Particles-Lung-Overload.pdf</url></related-urls></urls></record></Cite></EndNote>]), simulated epithelial lung fluid (SELF) (*e.g.*, Boisa *et al.* 2014 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and/or phagolysosomal simulant fluid (*e.g.*, BAUA, 2017 [ADDIN EN.CITE <EndNote><Cite><Author>BAUA</Author><Year>2017</Year><RecNum>57</RecNum><DisplayText>[33]</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595794599">57</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>BAUA</author></authors></contributors><titles><title>Methodology for the Identification of Granular Biopersistent Particles (GBP) at Workplaces</title><secondary-title>Federal Institute for Occupational Safety and Health</secondary-title></titles><periodical><full-title>Federal Institute for Occupational Safety and Health</full-title></periodical><pages>103, https://www.baua.de/EN/Service/Publications/Report/F2336.pdf</pages><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>])

- Employ a simple exponential decay model to predict the dissolution half-life: $P(t)=P0e^{-rt}$, where: P(t) = the amount of some quantity at time t; P0 = initial amount at time t = 0; r = the decay rate; t = time

The exponential decay function is the solution to the first order reaction equation, assuming a constant decay rate, r:

$$\frac{dP(t)}{dt} = -rP(t), P(0) = P_0$$

First order kinetics are used as the basis for lung clearance rates including dissolution and absorption into blood [ADDIN EN.CITE ADDIN EN.CITE.DATA].

- If the solubility data indicate a dissolution rate (*i.e.*, 100 mg/L/day or 72 mg/day) higher than the daily occupational exposure estimate (*e.g.*, default PDR of 50 mg/day), then stop at Tier I.
- If the solubility data indicate a dissolution rate lower than the daily occupational exposure estimate, then proceed with Tier II testing.

If the % of respirable particles is > 1 wt%, the HMW polymer is non-reactive, and the HMW polymer has a dissolution rate that is lower than the estimated daily occupational exposure estimate, proceed to Tier II.

Tier II

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- Perform computational modeling (*e.g.*, MPPD) ~~including the effect of dissolution~~ to predict deposition, clearance, and lung burden for a simulated chronic rat exposure (See, *e.g.*, Ladics *et al.*, 2020 [ADDIN EN.CITE

<EndNote><Cite><Author>Ladics</Author><Year>2020</Year><RecNum>69</RecNum><DisplayText>[23]</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838584">69</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ladics, G.</author><author>Price, O.</author><author>Kelkar, S.</author><author>Hermkimer, S.</author><author>Anderson, S.</author></authors></contributors><titles><title>In silico Multiple-Path Particle Dosimetry Modeling of the Lung Burden of a Biosoluble, Bioaccessible Alpha 1,3 Polysaccharide Polymer</title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>In preparation</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]). If dissolution data are not available, assume the test substance is poorly soluble.

- If the ~~clearance t½ is less than 60 days~~MPPD simulations do not indicate overload under the conditions of use, stop at Tier II.

If the ~~clearance t½ is greater than that for PSPs in the rat (*i.e.*, 60 days)~~ simulations indicate overload under the conditions of use, consider risk management options (*e.g.*, engineering controls and personal protective equipment) or proceed to Tier III.

Tier III

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- Strategic *in vivo* testing should be considered, albeit on a case-by-case basis, and after discussions with EPA at a pre-notice consultation meeting. When performed, the testing should include:
    - MPPD simulations to predict for the specific particle size, distribution, and density of the new chemical substance to identify exposure levels where overload is likely to occur.
    - Exposure at concentrations that allow for a concentration-response for low exposures, where pulmonary clearance is not impaired, and a high ~~enough to~~exposure that demonstrates impaired pulmonary clearance of particles and lead to an "overload" condition. It has been shown that in rats impaired clearance starts when phagocytized particle volume exceeds 6% of normal alveolar macrophage volume and clearance stops altogether when phagocytized volume reaches 60% of normal macrophage volume (See, *e.g.*, Borm *et al*., 2015 [ADDIN EN.CITE ADDIN EN.CITE.DATA]); and
    - Special attention to pulmonary function tests; blood oxygen (pO_2); lung burden measurements and lung clearance kinetics; collection of BALF for assessment of marker enzyme activities, total protein content, and cell counts; lung retention and clearance; lung weight; and lung histopathology (inflammation and cell proliferation). It is not necessary to evaluate internal organs. OECD TG 413 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>71</RecNum><DisplayText>[66]</DisplayText><record><rec-number>71</rec-

number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595838832">71</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>90-Day (Subchronic) Inhalation Toxicity Study</title><secondary-title>OECD Guideline for Testing of Chemicals</secondary-title></titles><periodical><full-title>OECD Guideline for Testing of Chemicals</full-title></periodical><pages>23, https://www.oecd-ilibrary.org/environment/test-no-413-subchronic-inhalation-toxicity-90-day-study_9789264070806-en</pages><volume>413</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] and OECD GD 39 [ADDIN EN.CITE <EndNote><Cite><Author>OECD</Author><Year>2018</Year><RecNum>72</RecNum><DisplayText>[67]</DisplayText><record><rec-number>72</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595839002">72</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>OECD</author></authors></contributors><titles><title>Guidance Document on Inhalation Toxicity Studies, Series on Testing and Assessment (Second Edition)</title><secondary-title>Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on

Chemicals, Pesticides and Biotechnology</secondary-title></titles><periodical><full-title>Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology</full-title></periodical><pages>106, https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)28/rev1&doclanguage=en</pages><volume>ENV/JM/MONO(2009)28/REV1</volume><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] should be consulted, given that the 90-day subchronic inhalation toxicity study in rats (OECD 413) with a 60-day recovery period is sufficient for identifying lung overload for PSPs in this species [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>32</RecNum><DisplayText>[2]</DisplayText><record><rec-number>32</rec-number><foreign-keys><key app="EN" db-id="xs0a90va7aasfwex5aev0dvyp0t59sta5dae" timestamp="1595769245">32</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200

Commented [ST7]: Comment from Anne: "There are also data to support using a 5 day exposure followed by a 28 day recovery may be sufficient to evaluate lung overload in PSP?"

TS: See included text. I modified this slightly from Ann's proposal.

Pennsylvania Ave., NW, Washington, DC 20460</full-title></periodical><pages>https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Research is ongoing to evaluate if studies utilizing shorter exposure duration (*e.g.*, 5 days) followed by recovery may be useful; therefore, if submitters are interested in evaluating the utility of a shorter duration study, such studies should be discussed with EPA prior to study initiation.

CONCLUSIONS

In summary, the available toxicological studies on HMW polymers support that the key parameters for determining whether a HMW polymer may present a hazard based on lung overload include: respirability, reactivity, and solubility. These are the same key parameters for lung overload caused by poorly soluble particles (PSP), an extensively studied and ~~well known~~well-known phenomena. ~~-~~The tiered strategy~~approaches~~ proposed in this ~~paper~~article takes advantage of these key factors and evaluates ~~identified for lung overload and apply, as~~their applicable~~ility~~ to HMW polymers. ~~—~~Two HMW polymers were ~~-~~identified as toxicological analogues ~~were identified -~~that may be used for "read across" when evaluating the potential of a ~~to~~ new chemical substance ~~for evaluating~~to result in lung overload. When applicable, the PODs on these analogues may be refined using dosimetry modeling such as simulations with the MPPD model to predict ~~when~~the exposure levels when overload might occur in the experimental species~~The MPPD software provides for a straightforward approach to predict when overload might occur in the experimental species~~, to perform interspecies extrapolation to HEC estimates,

and to inform inferences for human health risk ~~evaluation~~assessment. For new chemical substances that are not suitable for read across from these toxicological analogues, or when a company prefers to provide data for its specific HMW polymer new chemical substance, the tiered-testing strategy described above provides a framework that minimizes the use of vertebrate animals, and takes advantage of new alternative ~~method~~assays to characterize ~~and~~ key events in a putative AOP for ~~from~~ PSP induced lung overload; ~~with~~while providing information which may be used to determine if there is a potential for ~~informing whether~~for new HMW polymers to present a hazard for lung overload under its condition(s) of use. ~~Concentrations at which overload was not achieved in the rat are relevant to human assessment, as are other endpoints other than tumors at overload.~~ Collectively, the read across approach, ~~Simulations~~ the MPPD model simulations, and the tiered-testing strategy represent a novel approach method that will aid with evaluating new chemical substances to ensure that they do not present an unreasonable risk to human health and advancing the understanding of inhaled particle toxicity~~would also be most useful to design of experiments before costly investments in inhalation studies are made~~. ~~-~~Using these approaches, data on the respirability, reactivity and solubility of HMW polymers will be evaluated by EPA and only when needed, on a case by case basis, will animal studies be considered and discussed with the new chemical substance manufacture. ~~and may also help to~~resulting in a reduction and ~~refinement~~refinement of ~~reduce and refine~~ the number of animals used. ~~-~~The tiered testing approach was developed based on the best available science currently available. ~~-~~It is expected that as new data ~~will be~~is provided to EPA through new substance notifications, ~~and will be evaluated as appropriate to determine if~~ the tiered testing framework ~~requires modification~~will be evaluated and updated as appropriate. ~~-~~This is in line with EPA's Strategic Plan to Promote the Development and Implementation of Alternative Test Methods.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information file contains the following:

Section 1. Systematic Literature Review

Section 2. Experimental Animal Inhalation Studies on HMW Polymers

Section 3. Benchmark Dose (BMD) Modeling Outputs

Section 4: MPPD Modeling Outputs

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ~~‡These authors contributed equally. (match statement to author names with a symbol)~~

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5 Testing Consortium sponsored an updated literature review by an independent third party.~~ACC sponsored the supplemental literature review conducted by an independent third party.~~

Notes

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views or policies of their respective employers. Mention of trade names or commercial products does not constitute endorsement for use.

~~**ACKNOWLEDGMENT**~~

~~Generally, the last paragraph of the paper is the place to acknowledge people, organizations, and financing (you may state grant numbers and sponsors here).~~

REFERENCES

[ADDIN EN.REFLIST]

SUPPORTING INFORMATION FOR "POLYMER LUNG OVERLOAD CATEGORY: THE APPLICATION OF NEW APPROACH METHODOLOGIES (NAMS) FOR ASSESSING INHALATION RISKS UNDER THE AMENDED TOXIC SUBSTANCES CONTROL ACT"

1. SYSTEMATIC LITERATURE REVIEW

A. Initial Literature Search

i. Search Strategy

Computerized literature searches were initially conducted in PubMed in November 2016 to obtain studies related to lung overload from inhalation with the intention to identify, in further steps, those relevant for HMW polymers. Since "overload" is defined differently in experimental animals versus humans (Gregoratto et al., 2010, 2011; Kuempel et al., 2001a,b; Sweeney et al., 2013), general MeSH and query terms (*e.g.*, "Lung") and in text words (*e.g.*, "overload") were used with the intent of being overly inclusive. The search query string is presented in [REF _Ref46547342 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. PubMed search strategy for lung overload.

Database Search Date	**Query String**[a]
PubMed 11/15/2016	(Aerosols[mh] OR Particulate Matter[mh] OR Dust[mh] OR Lung[mh] OR Lung Diseases/Chemically Induced[mh]) AND Overload[tw]) NOT (Iron[mh]OR Calcium[mh] OR Heart[mh] OR Cardiac[tw])

[a] Note, in the Supplemental Literature Search performed on April 13, 2018, a more comprehensive list of MeSH, query, and text words was included (*e.g.*, "Particle", "Burden", "Retention", "Clearance", *etc.*).

Screening methods for this search included manual screening of titles/abstracts and screening of full text articles using the PECO criteria shown in [REF _Ref46547473 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. PECO criteria used to screen literature search results for lung overload

PECO element	**Evidence**[a]
Population	Humans, laboratory animals (rats, mice, hamsters, guinea pigs, dogs, non-human primates, or other inbred mammals) and mammalian cell lines
Exposure	*In vivo* (all routes), *ex vivo* (isolated perfused lung), and *in vitro*
Comparison	Any comparison (across dose, duration, or route) or no comparison (e.g., case reports without controls)
Outcomes	Any examination of: • Pulmonary effects *in vivo* or *ex vivo* studies • Cytotoxicity or alternative methods in *in vitro* studies

[a] The PECO criteria were refined and more specific in the Supplemental Literature Search performed on April 13, 2018 and included, for example, clearance parameters under the PECO element for "Outcomes".

ii. Additional Search Strategies

A search of the gray literature[1] was performed in September 2018 to obtain additional information pertaining to

[1] Gray literature, as used herein, has the same meaning as defined by EPA (2018) and "refers to sources of scientific information that are not formally published and distributed in peer-reviewed journal articles. These references are still valuable and

lung overload from poorly soluble HMW polymers. Resources searched for pertinent gray literature are listed in [REF _Ref46547609 \h * MERGEFORMAT] The chemicals and compound groups identified from the Initial Literature Search and used for gray literature searching are listed in [REF _Ref46547652 \h * MERGEFORMAT]. Screening methods for this search included manual screening of titles/abstracts and full text reports using the PECO criteria shown in [REF _Ref46547473 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. List of resources searched for gray literature.

ATSDR [HYPERLINK "http://www.atsdr.cdc.gov/toxprofiles/index.asp"]
Chemtrack [HYPERLINK "http://www.chemtrack.org/White/CMR.pdf"]
CIR [HYPERLINK "http://www.cir-safety.org/ingredients"]
ECETOC publications [HYPERLINK "http://www.ecetoc.org/publications"]
ECHA [HYPERLINK "http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances"]
EFSA (European Food Safety Authority) [HYPERLINK "http://www.efsa.europa.eu/"]
EPA – ChemView (incl. TSCATS data) [HYPERLINK "https://chemview.epa.gov/chemview"]
EPA – HPV Hazard Characterization Documents [HYPERLINK "http://iaspub.epa.gov/oppthpv/hpv_hc_characterization.get_report?doctype=2"]
EPA – HPV Risk-Based Prioritization Documents (RBPs) [HYPERLINK "http://iaspub.epa.gov/oppthpv/hpv_hc_characterization.get_report?doctype=1"]
EPA – HPVIS via ChemID - [HYPERLINK "https://chem.nlm.nih.gov/chemidplus/chemidlite.jsp"]
EPA – TSCATS 1 (available via Toxline)
EPA – pesticides - [HYPERLINK "https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1"] Archive [HYPERLINK "https://archive.epa.gov/pesticides/reregistration/web/html/status.html"]
FDA [HYPERLINK "https://www.fda.gov/default.htm"]
HERA [HYPERLINK "http://www.heraproject.com/RiskAssessment.cfm"]
HSDB [HYPERLINK "http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB"]
INCHEM (CICADS, EHC, HSG, IARC, IPCS, JECFA, SIDS) [HYPERLINK "http://www.inchem.org/"]
JECDB (Japan Existing Chemical Data Base) [HYPERLINK "http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp"]
NICNAS http://www.nicnas.gov.au/
NITE [HYPERLINK "http://www.safe.nite.go.jp/jcheck/search.action?request_locale=en"]
NTP [HYPERLINK "https://ntpsearch.niehs.nih.gov/home"]
OECD [HYPERLINK "http://www.echemportal.org/echemportal/page.action?pageID=9"]
OECD/SIDS [HYPERLINK "http://webnet.oecd.org/hpv/ui/SponsoredChemicals.aspx"]

consulted in the TSCA risk evaluation process. Examples of gray literature are theses and dissertations, technical reports, guideline studies, conference proceedings, publicly-available industry reports, unpublished industry data, trade association resources, and government reports."

Table [SEQ Table * ARABIC]. List of resources searched for gray literature.

ATSDR = Agency for Toxic Substances and Disease Registry; CICADS = Concise International Chemical Assessment Document; CIR = Cosmetic Ingredient Review; ECETOC = European Centre for Ecotoxicology and Toxicology of Chemicals; ECHA = European Chemicals Agency; EFSA = European Food Safety Authority; EHC = Environmental Health Criteria; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HERA = Human and Environmental Risk Assessment; HPV = High Production Volume; HPVIS = High Production Volume Information System; HSDB = Hazardous Substances Data Bank; HSG = Health and Safety Guideline; IARC = International Agency for Research on Cancer; INCHEM = Internationally Peer Reviewed Chemical Safety Information; IPCS = International Programme on Chemical Safety; JECDB = Japan Existing Chemical Data Base; JEFCA = Joint Expert Committee on Food Additives; NICNAS = National Industrial Chemicals Notification and Assessment Scheme; NITE = National Institute of Technology and Evaluation; NTP =National Toxicology Program; OECD = Organisation for Economic Cooperation and Development; SIDS = Screening Information Data Set; TSCATS = Toxic Substances Control Act Test Submissions

Table [SEQ Table * ARABIC]. Polymer lung overload chemical groups, constituent names, and CASRNs used for searching gray literature.

Chemical Group or Constituent Name	**CASRN**
Styrene/butylmethacrylate random copolymer	25213-39-2[2]
Polyvinyl chloride powder	9002-86-2
Polystyrene spheres	9003-53-6
Linear anionic hexamethylene diisocyanate monomer-based polyurethane-polyurea HMW polymer	No data
Acrylate copolymer	25053-63-8
Butyl acrylate/methacrylic acid polymer	25852-37-3

The reference lists of the primary studies and review articles identified by the PubMed search were manually screened to identify additional pertinent literature for lung overload from HMW polymers (*i.e.*, tree searching). A Supplemental Literature Search was performed in April 2018. The details of this search are provided in the section titled "Supplemental Literature Search". The Supplemental Literature Search was used to identify additional studies or data related to lung overload from HMW polymers that became available after the original search was conducted.

iii. Literature Search and Screening Results

The results of the literature search and screening effort are presented graphically in **[REF _Ref46547725 \h * MERGEFORMAT]**. The PubMed search identified 28 potentially relevant references for full text review. The PubMed search results were supplemented by a review of the reference lists from the relevant publications (*i.e.*, tree searching) which yielded an additional eight references for full text review. An additional four references were obtained from the search of gray literature resources, and the updated literature search identified nine additional references for full text review. Finally, two recent reviews were identified by unstructured PubMed searching.

The full text review of 51 references yielded 24 studies, which consisted of 16 potentially relevant studies with primary data on lung overload from poorly soluble HMW polymers, four studies with supporting information, and four relevant, recent reviews (*i.e.*, references cited in this paper). Twenty-seven articles were excluded. Nineteen of the articles were older or irrelevant reviews. One article, an *in vitro* study, was excluded after full-

[2] The TSCA inventory name for this CASRN is 2-Propenoic acid, 2-methyl-, butyl ester, polymer with ethenylbenzene.

text review (Konczol et al., 2013) because the study authors used a test substance (*i.e.*, carbon-bearing particles covered with submicron sized Fe_2O_3 particles) that was outside the category boundaries. Seven *in vivo* studies were excluded because the test materials studied were not relevant to the category (*e.g.*, silica, carbon black, and diesel exhaust particulates).

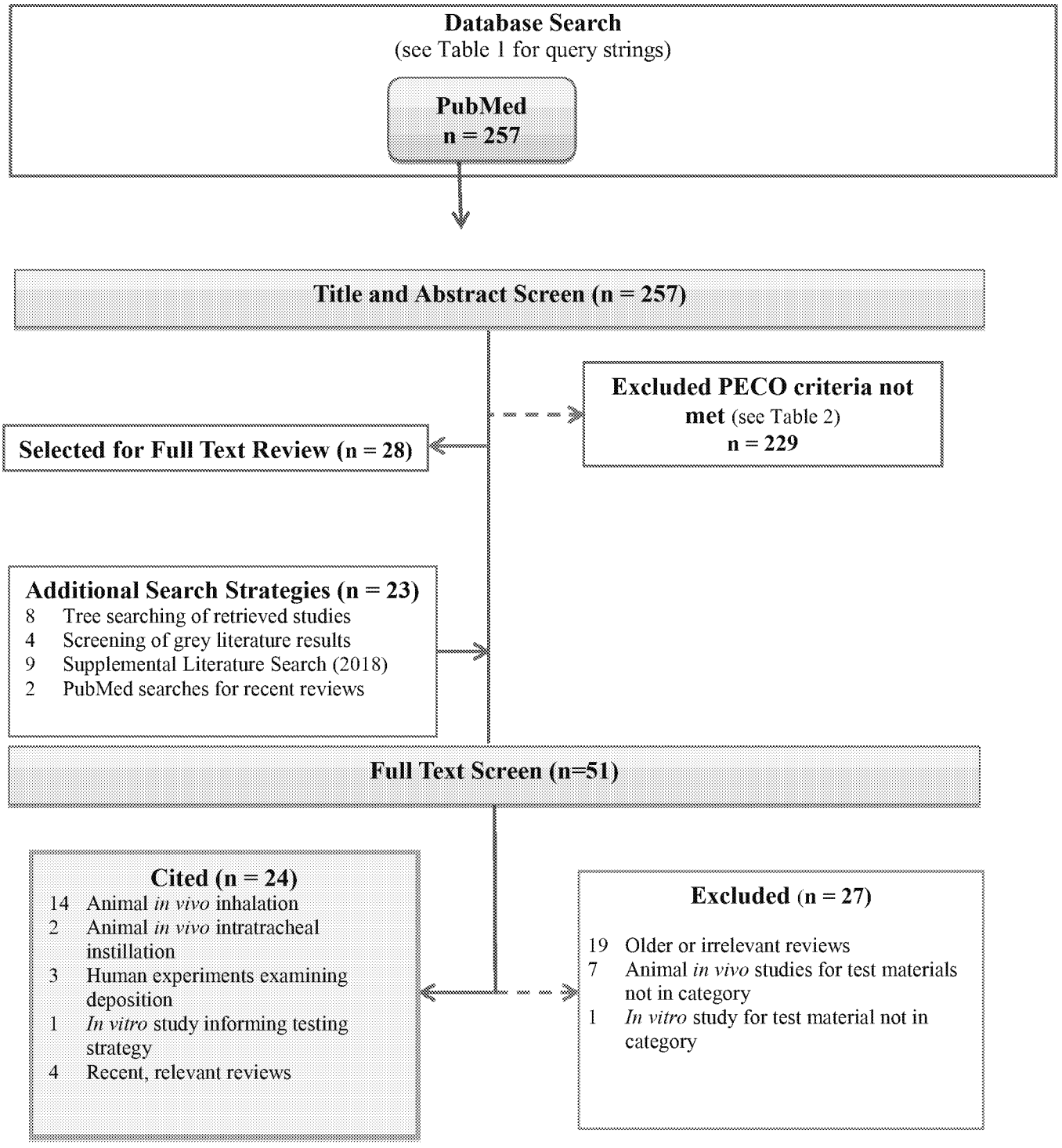

Figure [SEQ Figure * ARABIC]. Literature search and screening flow diagram for lung overload from HMW polymers.

B. Supplemental Literature Search

i. Search Strategy

To identify hazard concerns associated with inhalation exposure to poorly soluble polymers that would be in the category of polymer lung overload, the search strings presented in [REF _Ref46547800 \h * MERGEFORMAT] and [REF _Ref46547863 \h * MERGEFORMAT] were used for PubMed and Embase, respectively, to be more comprehensive. The results for this review are presented in [REF _Ref46548065 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. PubMed Search strategy for polymer lung overload.

(((Aerosols[mh] OR polymers[mh] OR polyacrylate* OR methacrylate OR methacrylate[mh] OR polyvinyls OR polyvinyls[mh] OR "polyvinyl chloride"[mh] OR polystyrenes[mh] OR (toner AND (plastic OR printer OR powder OR xenograph*))) AND ("particulate matter"[mh] OR "particulate matter"[tw] OR dust[mh] OR dust OR particulate OR particle OR respirable OR insoluble OR "high molecular weight") AND (overload[tw] OR Lung diseases/chemically induced[mh] OR "pulmonary toxicity" OR "pulmonary function test" OR "pulmonary function tests" OR "respiratory function tests"[mh] OR "bronchoalveolar lavage fluid"[mh] OR "alveolar macrophage-mediated clearance" OR (lung[mh] AND (burden OR retention OR clearance OR absorption[mh] OR inflammation OR inflammation[mh] OR fibrosis OR fibrosis[mh] OR neoplasms OR neoplasms[mh] OR "cell proliferation"[mh] OR weight OR histopathology OR irritants[mh] OR irritancy OR irritation))) AND (((exposure OR administration) AND (intratracheal OR intranasal OR inhalation*)) OR "inhalation exposure"[mh] OR "in vitro" OR "in silico"))) OR (lung[tw] AND particle[tw] AND overload[tw]) NOT (iron[mh] OR calcium[mh] OR heart[mh] OR cardiac[tw] OR copper[mh] OR wildfire) AND English[lang]

Table [SEQ Table * ARABIC]. Embase Search strategy for polymer lung overload.

(lung AND particle AND overload OR (('aerosol'/exp OR 'polymer'/exp OR polyacrylate* OR methacrylate OR 'methacrylic acid'/de OR polyvinyls OR 'polyvinylchloride'/exp OR (toner AND (plastic OR printer OR powder OR xenograph*))) AND ('particulate matter'/exp OR 'particulate matter' OR 'dust'/exp OR dust OR particulate OR particle OR respirable OR insoluble OR 'high molecular weight') AND (overload OR 'lung disease'/exp OR 'pulmonary toxicity' OR 'pulmonary function test' OR 'pulmonary function tests' OR 'lung function test'/exp OR 'bronchoalveolar lavage fluid'/exp OR 'alveolar macrophage-mediated clearance' OR ('lung'/exp AND (burden OR retention OR clearance OR absorption OR inflammation OR 'inflammation'/exp OR fibrosis OR 'lung fibrosis'/exp OR neoplasms OR 'neoplasm'/exp OR 'cell proliferation'/exp OR weight OR histopathology OR 'irritant agent'/de OR irritancy OR irritation))) AND ('in vitro' OR 'ex vivo' OR 'in silico' OR 'inhalation'/exp OR ((exposure OR administration) AND (intratracheal OR intranasal OR inhalation*))))) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND 'article'/it AND [english]/lim

ii. Study question and PECO criteria

The study objective was to identify properties of particles that fall into the polymer lung overload chemical category and cause lung toxicity from particle overload and impaired clearance following inhalation exposure. The study question was:

> What are the physical-chemical properties of insoluble, high-molecular-weight polymer particles that result in particle overload corresponding to measures of lung toxicity (*i.e.*, chronic inflammation, cell proliferation) following exposure *via* inhalation?

A study reported in the peer-reviewed literature was determined to be relevant and selected for full-text review, or excluded, based on the PECO criteria outlined in **[REF _Ref46548160 \h * MERGEFORMAT]**, in which study populations, study design, comparison groups, and measured outcomes are identified. Studies identified for full-text review were not scored for quality, but were reviewed with quality in mind to provide critical information that supports the relationship between decreased particle clearance, particle overload, and lung effects (*i.e.*, chronic inflammation, cell proliferation, fibrosis, *etc.*), which is the proposed mode of action for this category. Exposure levels at which toxicity occurs, along with responses that may be influenced by factors such as particle

characteristics were indicated as relevant information for capture to address the study question. Included in this assessment were other routes of administration that have been used to evaluate particle overload in animal models, such as intratracheal and intranasal administration.

Table [SEQ Table * ARABIC]. PECO criteria for polymer lung overload.

Population	Humans and animal models that characterize lung polymer particle clearance kinetics and toxicity, or *in vitro* study models that inform lung toxicity related to kinetics or toxicity Exclude: unhealthy human populations; disease-induced experimental animals
Exposure	Inhalation exposure (including intratracheal and intranasal administrations) to particles that are classified as insoluble, high-molecular-weight polymers
Comparator	No particle exposure (*i.e.*, room air or no exposure), vehicle control (including intratracheal and intranasal administration and *in vitro* studies)
Outcome	Properties of polymer particles, lung particle overload, polymer particle clearance kinetics, or lung toxicity

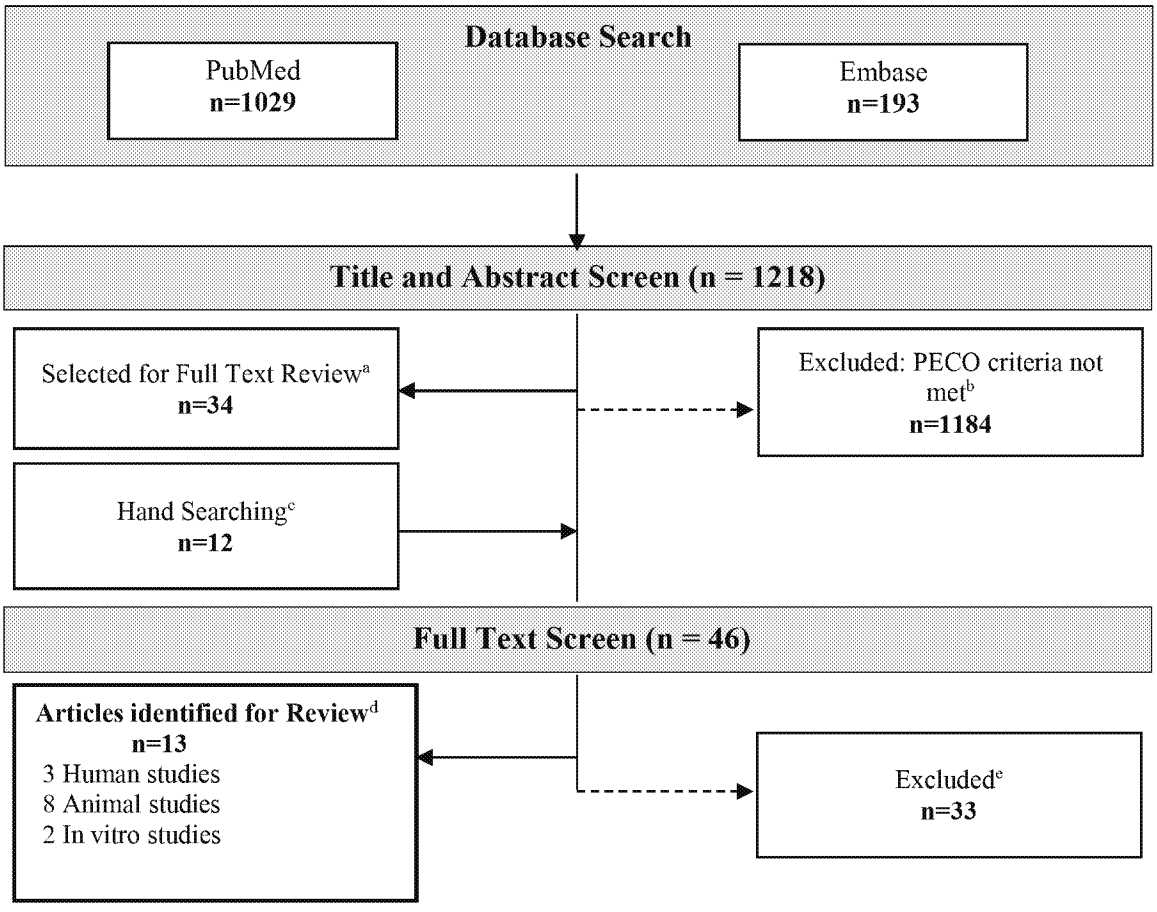

Figure [SEQ Figure * ARABIC]. Polymer lung overload: search strategy and results. [a] Selected based on title and abstract screen; [b] Excluded based on title and abstract screen; [c] Identified by hand-searching, either found in articles reviewed, or identified in the Initial Literature Search; [d] Studies identified as relevant for integrating into hazard summary; and [e] Key studies and review articles saved and used for contextual information are separately in the reference list.

iii. Hazard concerns

The hazard concerns associated with exposure to polymer lung overload particles are limited to effects on the lungs as a result of inhaling the particles. The substance may overload clearance mechanisms of the lung/respiratory system, resulting in effects that range from inflammation to fibrosis of the lungs often lead to altered lung function. There is a concern that the induction of chronic inflammation and fibrosis with chronic exposure, would result in lung cancer. Although carcinogenic effects have been demonstrated for poorly soluble inorganic particles, this has not been the case for the poorly soluble polymers defined in this chemical category. In a workshop hosted by ILSI and published in 2000 (ILSI, 2000), it was stated, "Because it is still not known with certainty whether high lung burdens of poorly soluble particulates can lead to lung cancer in humans via mechanisms similar to those of the rat, in the absence of mechanistic data to the contrary it must be assumed that the rat model can identify potential carcinogenic hazards to humans."

The review by ILSI (2000) stated that in the rat model, responsiveness to overload is associated with chronic inflammation and cell proliferation; therefore, when particle dose levels occur where these measures of response are not increased, it is anticipated that exposure would not result in lung tumors. This particle overload mode of action includes key events such as decreased lung particle clearance, retained particle burden in the lung that

exceeds a certain threshold, impairment of alveolar macrophage (AM) clearance function, AM accumulation, pulmonary inflammation, alveolar epithelia hyperplasia (proliferation), metaplasia, fibrosis, and possibly induction of lung tumors (reviewed by Borm et al., 2015; Warheit et al., 2016). A very thorough review of the pathobiology of lung overload is also presented in an ECETOC technical report (2013) which outlines the impact of biosolubility of the particles on their ability to be cleared. In short, poorly soluble particles that are inhaled are removed mainly by AM clearance and not by dissolution.

At the center of the particle overload hypothesis is the question about the human relevance of both non-neoplastic and neoplastic effects observed specifically in rats chronically exposed to high concentrations of poorly soluble particles of low acute toxicity (Borm et al., 2015). In the more recent review by Warheit et al. (2016), critical insights on differences in pulmonary response between rat exposure studies and occupationally exposed humans are identified. Although this review focuses on particle overload with inorganic particulates such as TiO_2, the species differences for particle deposition and overload for identification of hazard concerns for these and polymer lung overload particles, as defined in this category, are the same. These factors are critical considering that, at this time, it is still proposed that rat studies be used to evaluate hazard concerns for occupationally exposed workers. Considerations for evaluating lung effects from exposure to polymer lung overload in rats for extrapolation to humans include:

- Interspecies differences in lung responses of rats versus other rodents
- Interspecies differences in inhaled particle kinetics in rats versus nonhuman primates and humans that trigger particle-related responses in the lung
- Critical advancements in understanding the human respiratory tract and models of deposition and retention; used for simulating realistic particle translocation and retention
- Morphological differences and characteristics of rats for human lung tumor types and locations in the respiratory tract
- Epidemiological data from production works that demonstrate no correlation between particle exposure and lung cancer or other non-malignant respiratory diseases

Consideration of these differences between rodents and humans is at the core of this Supplemental Literature Review, especially when recommendation of further testing in the rat model is proposed. A tabular summary of peer-reviewed publications identified for full-text review is provided in [REF _Ref46548287 \h * MERGEFORMAT]. Study summaries with respect to the PECO criteria identified in this Supplemental Literature Review are provided below by study category (*i.e.*, human, animal *in vivo,* and *in vitro*) and are summarized with general comparisons to the findings presented in the Initial Literature Search. Critical information was documented that drove data collection for the development of a database of identified parameters associated with the hazards of concern for the polymer lung overload chemical category.

Given the limited information available in the literature for both human and *in vitro* studies on polymer lung overload particles as defined, selected particles that would not necessarily be included in this chemical category were considered for the Supplemental Literature Review, as the identified studies may be relevant concerning particle clearance kinetics or potential *in vitro* assay systems for consideration in an alternative non-animal testing strategy.

Table [SEQ Table * ARABIC]. Peer-reviewed publications identified for full-text review.

Author/Title	Defined test substance	Particle characteristics (physical form, Molecular weight, *etc.*)	Study type / Model	Exposure route / concentrations	Study description	Aerosol / particle size	Outcomes / Toxicity	Authors' conclusions
Bai et al., 2010. Pulmonary responses to printer toner particles in mice after intratracheal instillation.	Toner; collecting during a printing process $PM_{2.5}$ and PM_{10}	N/A	*In vivo* / male ICR mice	Intratracheally instillation/40 mg/kg	Instillation of dose formulation was performed 4 times (every 2 days). Toxicity evaluation was conducted at 9, 28, 56, and 84 days post instillation. Control group - no instillation. The pulmonary responses were measured bronchoalveolar lavage fluid (BALF) for biochemical analysis and lung tissue histopathology and electron microscopy.	The toner particles administered to the animals were not clearly defined, assumed to be $PM_{2.5}$ and PM_{10}	It was noted that during the experimentation period toner particles were shown to adhere to the alveolar septal walls and enter into the alveoli to cause pulmonary lesions. Lung overloaded by toner particles caused an inflammatory response and damaged alveolar epithelial -capillary barrier and increased cell permeability. Although this type of administration does not provide realistic exposure and lung burden/clearance data, it does confirm that damage that occurs where particles are administered to the lung.	Authors state "The results of biochemical analysis of BALF and lung homogenates indicated that the lung were overloaded by toner particles, which induced inflammatory response, damaged alveolar epithelial-capillary barrier and increased cell permeability. The increased phagocytosis of particles by AMs in lungs was observed over time. The normal lung structure was damaged simultaneously. In this study, we did not find pulmonary fibrosis or mesothelioma formation throughout the experiment."
Bellman et al., 1991. Lung clearance and retention of toner, utilizing a tracer technique, during chronic inhalation exposure in rats. **Identified in Initial Literature Search.**	Only identified as "Special Test Toner"	N/A	*In vivo*, male and female F344 rats	Inhalation exposure, 0, 1, 4, 16 mg/m^3 - toner and TiO_2 at 5 mg/m^3 or SiO_2 at 1 mg/m^3.	Rats exposed *via* exposed 6 hr/day, 5 days/week up to 24 months - pulmonary retention measured after 3, 9, 15, 21 and 24 months	Mass median aerodynamic diameter (MMAD) was geometric standard deviation of not identified	The final pulmonary burdens of toner at the 3 exposure levels were 0.22, 1.73, and 15.6 mg/lung. Clearance was impaired at the mid- and high exposure level. Both the maximum tolerated dose and the maximum functionally tolerated dose were exceeded at the toner high exposure level during the study in rats. MTD and MFTD is based on clearance - Boundaries for safety would have to be determined to ensure	As noted by the authors, alveolar clearance of toner was impaired at the high, and moderately slowed at the mid exposure levels. At high-exposure it was associated with lung overloading. For inhalation of insoluble particles Muhle et al. 1990 suggested the use of maximum functionally tolerated dose (MFTD) concept, in terms of a lung burden at which macrophage-mediated clearance half-time is increased by a factor of 2-4.

							exposure levels over a period of time would be able to be cleared, etc. Note: Based on the lack of toner particle information and the lack of response data- this article was extracted but does not provide all necessary information for an evaluation.	
Bellman et al., 1992. Irreversible pulmonary changes induced in rat lung by dust overload. **Identified in Initial Literature Search.**	9000-type xerographic toner material composed of 90% styrene/1-butylmethacrylate random copolmer-with 10% high purity furnace type carbon black [CAS 25213-39-2/ 7440- 44-0]	N/A	*In vivo* / female F-344 rats	Inhalation exposure, 0, 10, 40 mg/m^3; methods described by Muhle et al., 1991	Rats exposed via nose-only inhalation 6 hrs/day, 5 days/wk, for 3 months at 4 doses (plus control). Recovery groups (4 wks recovery) were included in control and high dose groups. Clinical chemistry, tissue weights and histopathology were examined. Tracer aerosols were inhaled (NO) for 0.5-1.0 hr by eight animals for analysis of lung burden. Retention of test toner in the lungs and in the lung-associated lymph nodes was analyzed in lung tissue. BALF (cytology and cell toxicity measures, LDH, β-glucuronidase and total protein). The distribution of test toner particles in macrophages was analyzed by light microscopy. Lung tissue evaluated for histopathological changes. This study was conducted to investigate if toxicity associated with overload would be reversed following cessation of exposure and clearance of particles.	Mass median aerodynamic diameter (MMAD) was 4.0 µm with a geometric standard deviation of 1.5	Overall half-times of toner clearance were calculated as 277 and 2845 days at 10 and 40 mg/m^3, respectively. The retained test toner at the end of exposure was 0.4 and 3.0 mg in the lung for the low and high exposure groups, respectively. At the high exposure, LDH, β-glucuronidase and total protein were elevated with a minor recovery after 15 months. Differential cell count was only slightly increased in the number of PMN with significant response at the high concentrations. Alveolar clearance was delayed at the low exposure, but most completely impaired at the high exposure level with significance after 3 months.	As noted by the authors, in the high exposure group, the pattern of the effects during the 15 - month post-treatment observation period was similar (based on measures of toxicity). Much of these study findings were based on high exposure. It is critical to note that the 10 mg/m^3 exposure did not show changes in LDH, β-glucuronidase, and total protein

Klas et al., 2009. Does lung retention of inhaled particles depend on their geometric diameter?	^{111}In - Labeled polystyrene and Teflon particles	Densities of particles were 1.05 g/cm^3 for polystyrene and 2.13 g/cm^3 for Teflon.	Humans, 9 healthy nonsmokers	Length of inhalation exposure varied between 3- 5 minutes and number of inhalations between 4 and 6. Flow of 0.045 L/s. Note: focus on ciliary airways; Lung deposition was modeled.	Particle inhalation followed by radioactivity distribution at 24, 48, and 72 hours post exposure using NaI crystals fitted with collimators and profile scanning over the mouth, throat, lungs and stomach of each subject. Theoretical calculations of lung deposition were	Mean aerodynamic diameter is 6.2 and 6.5 µm for polystyrene and Teflon particles, respectively with the mean geometric diameter was 6.05 µm and 4.47 µm for the polystyrene and Teflon particles, respectively with the geometric standard deviation 1.06 for both.	Particle deposition in the lung averaged 20 and 68 (lung retention at 24 hours as a percental of initial lung deposition) for polystyrene and Teflon, respectively.	This study did not show evidence that the fraction of particles deposited in the conducting airways and their retention is dependent on geometric diameter in the size range studied. Note: when exposure is low particle overload that occurs in rat models cannot be evaluate in human studies.
Konczol et al., 2013. Oxidative stress and inflammatory response to preinter toner particles in human epithelial A549 lung cells	Printer toner powders Carbon-bearing particles (2–12 µm), rough surface covered with Fe_3O_4 sub-micron particles (30–200 nm); Presence of rutile, cristobalite, perovskite	N/A	*In vitro*, human epithelial A549 lung cells; human lung adenocarcinoma type-II alveolar epithelial cells	Particle suspensions in RPMI 1640 supplemented with 1% L-glutamine and 1% penicillin/streptomycin, 2.5 µL tween 20 for homogeneous dispersion	Cells were exposed to. Toner at 20-200 µg/cm^2 / 0 µg/cm^2 for up to 24 hours.	2–12 µm, particles 30–200 nm	Endpoints included mitochondrial membrane depolarization, NF-kB binding activity, IL-6 and IL-8 levels along with measures of cytotoxicity using water-soluble tetrazolium assay and neutral red uptake.	Overall exposure to these toner particle suspensions resulted in a concentration dependent formation of reactive oxygen species and measures of oxidative stress through induction of reactive oxygen species that could result in activation of pro-inflammatory pathways.
Lee et al., 1988. Lung response to ultrafine Kevlar aramid synthetic fibrils following 2-year inhalation exposure in rats.	Kevlar fibrils (<3.0 um in diameter) and < 100 µm in length	N/A	*In vivo*, male and female Crl:CD (SD)BR rats	Exposed by inhalation to ultrafine Kevalr fibrils at 2.5, 25 or 100 fibrils/cc	Rats were exposed for 6 hr/day, 5 days/week for 2 years. Lung response to ultrafine Kevlar synthetic fibrils following 2-year inhalation exposure in rats	Exposure to Kevlar fibers at 2.5 to 400 fibers/cc with a mean mass concentration of 0.08 to 2.23 mg/m^3. The fibril/mass ratio was 30 to 184.	Kevlar exposed rats did not develop mesothelioma or different histological types of lung tumors including papilloma, bronchioloalveolar adenoma, bronchogenic carcinoma, squamous cell carcinoma, fibrosarcoma, or adenocarcinoma. No pathological lesions attributable to Kevlar dust exposure in lungs, without	

							any observation of hyperplastic epithelial change nor inflammatory response to deposition. It is noted that the majority of Kevlar fibrils were phagocytized by single macrophages in the alveoli adjacent to the alveolar duct region. Note: particle deposition was confined to the alveolar duct region, particle overload was not identified by name, but this is an early publication. There is no evidence in this study that fiber overload was demonstrated with decreased clearance.	
Muhle et al., 1990a. Subchronic inhalation study of toner in Rats. **Identified in Initial Literature Search.**	9000-type xenographic toner material composed of 90% styrene/1-butylmethacrylate random co-polymer- with 10% high purity furnace type carbon black. The polymer was composed of styrene and 1-butylmethacrylate ratio of 58:42 [CAS no. 25213-39-1/ 7440-44-0]	MW 70,000 Daltons	*In vivo*, female F344 rats	Whole body, inhalation exposure/ 0, 4, 16, 64 mg/m^3 - corresponded to 0, 0.35, 1.4, 5.6, 22.4 mg/m^3 of respirable material	6 hr/day, 5 days/week for up to 13 weeks. Retention and clearance measurements after 30, 60 and 90 days at 1 and 64 mg/m^3 and after 45 and 90 days.	Mass median aerodynamic diameter (MMAD) was 4.0 µm with a geometric standard deviation of 1.5,	Lung weight and histopathology, respiratory volume and frequency, lung burden of toner, deposition rate, alveolar clearance and retention. Both wet and dry weights of left lung were elevated at highest concentration, with deposition of toner 5.8-fold higher at 64 v. 16 mg/m^3. Based on retention of toner, there was a greater than proportional increase retained at 16 and 64 mg/m^3 suggesting overloading. Clearance mechanisms were impaired at high exposures up to 90 days. Lungs had increased particle - laden macrophages with few in alveolar walls.	

Muhle et al., 1990b. Dust overloading of lungs after exposure of rats to particles of low solubility: Comparative studies. **Identified in Initial Literature Search.**	Test toner (carbon black pigmented acrylic polymer), polyvinyl chloride powder, carbon black (type 'Printex 90', and two modifications of TiO^2	N/A	*In vivo*, rats (limited reporting)	Exposure not described with concentrations reported as Toner 1, 4, 16.1, 63.2 mg/m^3, PVC 3.3, 8.3, 20.2 mg/m^3, Carbon black, 9 mg/m^3 compared to control 0 mg/m^3	Exposure for up to 2 years at selected time points.	Diameter (µm), MMAD (µm) geometric SD, density: Toner ~ 4, 4, 1.5, 1.15; PVC ~ 1.3, 1.3, 2.07, 1.3; Carbon black ~0.014, 0.96, 2, 2	Particle clearance, measures of cytology (BALF) lung histology. Exposure resulted in retardation of alveolar clearance when retained mass reached a level of 0.5 mg per rat lung with over 700 days of overloading (>10 mg per rat lung. After 24 months, an increase in PMN (polymorphonuclear cells) was observed at 4 and 16 mg/m^3.	"Characteristic findings of dust overloading of lungs are: (a) alveolar clearance retardation, (b) increased retention of material in the lung, (c) increase in lung weight, (d) accumulation of dust laden macrophages, (e) persistent inflammation, (f) increased epithelial permeability, and (g) elevated infiltration of neutrophils. Specific histopathological findings will be presented elsewhere."
Muhle et al., 1991. Pulmonary response to toner upon chronic inhalation exposure in rat s. **Identified in Initial Literature Search.**	Test toner [contained 90% random copolymer CAS No. 25213-39-2) and 10% high purity carbon black CAS No. 7440-44-0]; polymer composed of styrene and 1-butyl methacrylate (58:42)	Density 1.2 g/cm^3, MW 70,000 Daltons	*In vivo*, F344 male and female rats	Whole body inhalation exposure using a dry aerosol dispersion technique. Target concentrations 0, 1, 4, 16 mg/m^3 of toner.	Rats were exposed 6 hr/day, 5 days/wk for up to 24 months	MMAD ~ 4.0 µm with GSD of 1.5	BALF (cytology, LDH, β-glucuronidase, total protein), lung histopathology and lung were measured. Animals were reported to not show any clinical signs and appeared healthy at the end of exposure. Both absolute and relative lung weights were increased with increased retention of particles. Elevation in measured in BALF were observed with increased toner concentration. There was an exposure and time-dependent increase in the extent of particle-laden macrophages in lungs of toner-exposed rats. Toner increased primary lung tumors from 1 (adenoma) in the low dose to 3 tumors at the high concentration, without tumors identified in the mid concentration.	Author states "The appropriate manner to compare various dusts is by density-corrected mass or volume of material tin the lungs."

Oberdorster et al.; 1992. Volumetric loading of alveolar macrophages (AM): A possible bassi for diminished AM- mediated particle clearance. **Identified in Initial Literature Search.**	^{141}Ce-labeled 3.3 µm diameter and ^{95}NB-labeled 10.3 µm diameter polystyrene microspheres were obtained as dry particles.	N/A	*In vivo*, male Fischer 344 rats	Intratracheally instillation of polystyrene particles; 40 µg and 100 µg of 3.3 µm particles and 10 and 100 µg of 10.3 µm particles - mixture of ^{141}Ce and ^{95}NB-polystrene particles - Note: although useful in understand the mode of action, the exposure following intratracheally administration is different from inhalation exposure.	Animals were administered particles by intratracheal instillation and killed to evaluate lung retention, cytology measurements in lung lavage for particle recovery (did not work well) and histopathology at 132- and 202-days post administration.	Diameter 3.3 µm and10.3 µm; converting administered mass to volume; low dose received 2.2E7 µm^3 and the high dose group received ~1.1E8 µm^3.	Overall particle clearance was AM (alveolar macrophage) mediated with translocation through the tracheobronchial tree in the GI. The particle associated radioactivity in the BL was the same whether it was large or small particles. There was no histological evidence for particle sequestration suggested by the aggregation of AM.	Authors state "We conclude from these studies in the Fischer 344 rat that (1) large (10.3 µm) particles are readily phagocytized by AM, (2) phagocytized 10.3-pm particles significantly reduce AM clearance function, (3) pulmonary clearance of 3.3 µm and 10.3 µm particles at lung burdens of 100 µg/rat lung occurs *via* the tracheobronchial tree into the GI tract, and (4) our results support the volumetric hypothesis of retardation of AM-mediated particle clearance."
Smith et al., 2008. Effect of particle size on slow particle clearance from the bronchial tree	Nontoxic insoluble particles; ^{99}mTC and ^{111}In labeled polystyrene latex (PSL) and ^{198}Au labeled gold	PSL: density 1.05 g/cm^3; gold: density 19.3 g/cm^3	Healthy volunteers, non- or stopped smokers.	Particles were administered as a bolus of an aerosol into a specific depth of the lungs using a nebulizer, monitoring breathing and lung capacity, to obtain the required initial lung deposit of particles.		Aerodynamic diameter of 5 µm, Gold particles geometric diameter 1-2 µm with aerodynamic diameter of 4.9 µm	Study was designed to test the parameter of particle geometric diameter on clearance of particles form the bronchial tree. Although, clearance from the bronchial tree is not the mode of action of particle overload, information on particle diameters was of interest. In this study there was no difference in the retention of 1 µm gold particles and 5 µm polystyrene particles.	

Svartengren et al., 2001. Comparison of clearance of particles inhaled with bolus and extremely slow inhalation techniques.	Teflon particles labelled with ^{111}In	N/A	Human, 10 healthy nonsmoker volunteers	Volunteers inhaled Teflon particles labelled with ^{111}IN with a shallow bolus technique and an extremely slow (~0.05L/s) inhalation technique. There was an interval between the 2 inhalation exposures by 1 month	Following inhalations of either method, radioactivity in the lungs was measured at 1 and 24 hours, and then 1 2, and 3 weeks post exposure.	Geometric particle diameter was 4.4 µm with the GSD 1.05 for the bolus and 1.07 for the slow inhalation. MMAD was 6.4 µm	Forced vital capacity (FVC) Forced expiratory volume in 1 s (FEV1,0) and forced expiratory flow between 25 and 75% (FEF25-75%) of the exhaled volume was only used to compare subjects and parameters for modeling. Using a scan to follow deposition of radiolabeled particles and distribution in the lung was monitored. Bolus v. slow inhalation did not appear to change the lung deposition of these particles. Although clearance evaluated, the deposition of these particles was not in the alveolar space or appeared to be at the concentration where lung overload conditions, similar to what would occur in rats could be evaluated.	Bolus v. slow inhalation did not appear to change the deposition or extent of the particles to various lung regions.
Wiemann et al, 2016. An in vitro alveolar macrophage assay for predicting the short- term inhalaiton toxicity of nanomaterials. **Identified in Initial Literature Search.**	18 inorganic nanomaterials, covering AlOOH, $BaSO_4$, CeO_2, Fe_2O_3, TiO_2, ZrO_2, and ZnO NMs, amorphous SiO_2 and graphite nanoplatelets, and two nanosized organic pigments. ZrO_2 and amorphous SiO_2 were tested without and with surface functionalization. ***NOTE:*** This study does not meet the defined chemical category but was identified as a possible	N/A	*In vitro*, rat NR8383 alveolar macrophages	Test materials were incubated with cells in protein free culture medium	LDH, glucuronidase and tumor necrosis factor alpha, and ROS/H_2O_2 were used to monitor responses after 16 hours of exposure.	Size (nM), surface areas BET (m^2/g), size in buffer, (nm) and concentration in buffer; ranged from 2 nm to < 30 µm, 15 to 200 m^2/g, not detectable to 290 nm, not detectable to 1.3E8 particles/mL, respectively	Based on particle surface area threshold, there were low in vitro effects compared to materials above the threshold (6000 mm^2/mL) that result in overloading and were considered active (2 of the 4 toxicity parameters). Overall this assay was highly predictable of short-term rat inhalation hazard potential.	Authors state "When integrated into a tiered testing approach, such as the DF4nanoGrouping, the in vitro NR8383 AM assay may substantially reduce the need for animal testing addressing the inhalation route of exposure. Further work should aim at validating this assay."

	method to evaluate insoluble particles *in vitro*.							

iv. Studies in humans

The Initial Literature Search did not identify human studies that describe exposure to the particles defined in this polymer lung overload category. In the Supplemental Literature Search, several studies were identified in humans that did not necessarily fulfil all the PECO criteria ([REF _Ref46548160 \h * MERGEFORMAT]) but provided information on particle parameters and lung clearance in humans. The identified studies are summarized in [REF _Ref46548446 \h * MERGEFORMAT] according to these PECO criteria and used to highlight critical information and/or gaps in the knowledge base ([REF _Ref46548287 \h * MERGEFORMAT]).

The studies in humans, outlined in [REF _Ref46548287 \h * MERGEFORMAT], note that parameters of particle geometric diameter and density do not seem to play a role in lung clearance. It is important to note that conditions of particle overload in AM were not evaluated, as lung deposition was in the bronchial tree, where clearance mechanisms are different (Svartengren et al., 2001; Smith et al., 2008; Klas et al., 2009). As is obvious, particle lung overload experiments could not be conducted ethically in humans, because the mechanism of lung overload would be through high chronic exposure conditions. The more recent review by Warheit et al. (2016) references an epidemiological investigation of exposure to toner, in which an absence of lung cancer excess risk due to dust exposures was reported. This study was not captured in the Initial Literature Search or the Supplemental Literature Search, though its review may be of use for strengthening the discussion that these particles do not presence a cancer hazard.

Table [SEQ Table * ARABIC]. Population: Human studies on polymer lung overload.

Reference	Polymer lung overload Particles	Exposure/Comparator	Clinical Outcomes/Toxicities
Klas et al., 2009.	Radiolabeled polystyrene particles and ^{111}In-labeled Teflon particles	Length of inhalation exposure was 3–5 mins, between 4 and 5 inhalations at a flow of 0.045 L/s. Particle deposition in the lung averaged 20 and 68 (lung retention at 24 hours as a percentage of initial lung deposition) for polystyrene and Teflon, respectively. Note: exposure and comparator information not clearly identified with focus on ciliary airways.	This study did not show evidence that the fraction of particles deposited in the conducting airways, and their retention, depend on geometric diameter in the size range studied. Note: when exposure is low, particle overload that occurs in rat models cannot be evaluated in human studies.
Smith et al., 2008.	Nontoxic insoluble particles; ^{99}mTC and ^{111}In labeled polystyrene latex (PSL) and ^{198}Au labeled gold; Densities PSL: 1.05 g/cm^3, Gold: 19.3 g/cm^3	Particles administered as a bolus of an aerosol into a specific depth of the lungs using a nebulizer, monitoring breathing and lung capacity, to obtain the required initial lung deposit of particles. Gold: 1μm particles PSL: 5 μm particles	Study was designed to test particle geometric diameter on particle clearance from the bronchial tree. Although clearance from the bronchial tree is not the mode of action of particle overload, information on particle diameter and density was of interest. In this study, there was no difference in the retention of gold and PSL, particles of different densities and diameters.

Svatengren et al., 2001.	^{111}In-labeled Teflon particles	Volunteers inhaled ^{111}In labeled Teflon particles with a shallow bolus technique and an extremely slow (~0.05 L/s) inhalation technique; 1-month interval between two exposures, with lung radioactivity measured at 1 and 24 hours, and then at 1, 2, and 3 weeks post-exposure. Geometric particle diameter was 4.4 µm with the geometric standard deviation (GSD) 1.05 for the bolus and 1.07 for the slow inhalation. Mass median aerodynamic diameter (MMAD) was 6.4 µm.	Bolus v. slow inhalation did not appear to change the lung deposition of these particles. Although clearance was evaluated, these particles were not deposited in the alveolar space and appeared to be at the concentration where lung overload conditions, similar to what would occur in rats, could be evaluated.

v. Studies in animal and in vitro models

In vivo animal and *in vitro* studies are summarized in [REF _Ref46548546 \h * MERGEFORMAT] and [REF _Ref46548653 \h * MERGEFORMAT], respectively, according to the PECO criteria that were used to identify critical information and/or gaps in the knowledge base ([REF _Ref46548287 \h * MERGEFORMAT]).

In agreement with the findings from the Initial Literature Search, only limited information was identified in the Supplemental Literature Search which evaluated particles that induce adverse lung effects through overload and saturation of clearance mechanisms ([REF _Ref46548546 \h * MERGEFORMAT]). In summary, the older studies identified in the Initial Literature Search (Bellman et al., 1991, 1992; Muhle et al., 1990a,b, 1991) may have deficiencies in either study design and/or reporting, but they capture the dynamics of these particles in the lung and provide a foundation for establishing that the particle overload mode of action is driving the adverse effects following inhalation exposure to polymer lung overload particles.

In the search strategy employed in the Supplemental Literature Search, many of the same articles were identified from the Initial Literature Search, even though the search strategy was expanded to include other routes of administration, such as intratracheal instillation, in an effort to capture more data on particle characteristics, AM overload, and decreased clearance. One additional study was identified that met the PECO criteria in which rats were administered the test substance by intratracheal instillation (Bai et al., 2010). In comparison, one study was identified in the Initial Literature Search that evaluated polymer lung overload from a substance following intratracheal instillation (Oberdorster et al., 1992). There are a number of studies in the literature that administered particles via intratracheal instillation; however, these were not particles identified in the Initial Literature Search as within the polymer lung overload category. The study conducted by Oberdorster et al. (1992) supported that intratracheal instillation could be used to study the mode of action of particle lung overload induced lung toxicity. Although biosolubility of a particle has been identified as being critical to the particle overload mode of action, no information presented in the studies reviewed provided this type of information for the polymer lung overload particles tested.

Only two *in vitro* assays were identified in the Supplemental Literature Search with potentially useful information- one of which was originally identified in the Initial Literature Search (Wieman et al., 2016). Although Wieman et al. (2016) did not test particles that would meet the polymer lung overload category, the significance of this assay is that rat NR8383 alveolar macrophages were used, and therefore, a measure of particle clearance kinetics and toxicity could be evaluated. This assay was highly predictive of short-term rat inhalation hazard potential for inorganic particulates. The other *in vitro* assay identified in the Supplemental Literature Search (Konczol et al., 2013) used human epithelial lung cells (A549), since it does not include AM, necessary to capture the particle

lung overload mode of action, it might not be useful to evaluate polymer lung overload particles in this chemical category.

Table [SEQ Table * ARABIC]. Population: Animal studies on polymer lung overload.

Reference	Polymer lung overload particles	Exposure /Comparator	Outcomes/Toxicities
Bai et al., 2010.	Toner; collected during a printing process, $PM_{2.5}$ and PM_{10}	Mice, intratracheal instillation 4 times (every 2 days) and evaluated up to 84 days post-exposure at 40 mg/kg saline or no instillation. The toner particles administered to the animals were not clearly defined, assumed to be $PM_{2.5}$ and PM_{10}	Exposure to toner particles resulted in a significant inflammatory response and lung lesions associated with an increase in alveolar macrophage numbers with increased apoptosis.
Bellman et al., 1992. Identified in the Initial Literature Search	9000-type xerographic toner material composed of 90% styrene/1- butylmethacrylate random copolmer- with 10% high-purity furnace-type carbon black [CAS 25213-39-2/ 7440-44-0]	Rats, 6 hr/day, 5 days/week for 3 months, Inhalation exposure to aerosol 10, 40 mg/m^3 / 0 ppm. Mass median aerodynamic diameter (MMAD) was 4.0 μm, with a geometric standard deviation of 1.5.	Toner clearance half-times increased with exposure, 277 and 2845 days at 10 and 40 mg/m^3, with 0.4 and 3.0 mg lung burden at end of exposure. LDH, β-glucuronidase, and total protein increases showed a minor recovery after 15 months at the high concentration. Differential cell count was significantly increased at the high concentration; number of polymorphonuclear cells. Alveolar clearance was delayed at the low, but almost completely impaired at the high concentration after 3 months.
Bellman et al., 1991. Identified in Initial Literature Search Note: Based on the lack of toner particle information and the lack of response data, this article was extracted but does not provide all necessary information for an evaluation.	Only identified as "Special Test Toner"	Rats, exposed by inhalation at 6 hr/day, 5 days/week up to 24 months, 1, 4, 16 mg/m^3 / 0 mg/m^3; the final pulmonary burdens of toner at the 3 exposure levels were 0.22, 1.73, and 15.6 mg/lung. MMAD or GSD not provided.	Particle retention was evaluated; both the maximum tolerated dose (MTD) and the maximum functionally tolerated dose (MFTD) were exceeded at high exposure level. MTD and MFTD are based on clearance documented within the context of Muhle et al., 1991.

Konczol et al., 2013.	Carbon-bearing particles (2–12 μm); rough surface covered with Fe_3O_4 submicron particles (30–200 nm). Presence of rutile, cristobalite, perovskite.	*In vitro*, human epithelial A549 lung cells exposed to particle suspensions in media for up to 24 hours. Cells exposed to 20–200 $\mu g/cm^2$ / 0 $\mu g/cm^2$.	Exposure to toner particle suspensions showed a concentration dependence in measures of oxidative stress through induction of reactive oxygen species that could result in activation of pro- inflammatory pathways. Not evaluated with respect to particle lung overload.
Lee et al., 1988.	Kevlar fibrils	Rats were exposed for 6 hr/day, 5 days/week for 2 years to ultrafine Kevlar fibrils at 2.5, 25, or 100 fibrils/cc. Fibers <3.0 μm diameter and <100 μm length.	Kevlar-exposed rats did not develop mesothelioma, different histological types of lung tumors, or non- neoplastic lesions (hyperplastic epithelial change, nor inflammatory response to deposition) associated with exposure. Note: particle deposition was confined to the alveolar duct region; particle overload was not identified by name (early publication). There is no evidence in this study that fiber overload was demonstrated with decreased clearance.
Muhle et al., 1990a. Identified in the Initial Literature Search	9000-type xenographic toner material composed of 90% styrene/1-butyl- methacrylate random co-polymer, with 10% high-purity furnace- type carbon black. The polymer was composed of styrene and 1-butyl- methacrylate ratio of 58:42 [CAS no. 25213-39-1/ 7440-44-0]	Rats, 6 hr/day, 5 days/week for 13 weeks. Inhalation exposure to aerosol 4, 16, or 64 mg/m3 / 0 ppm. Mass median aerodynamic diameter (MMAD) was 4.0 μm, with a geometric standard deviation (GSD) of 1.5.	Both wet and dry lung weight was elevated at 64 mg/m^3, with deposition of toner 5.8-fold higher at 64 vs 16 mg/m^3. Based on retention of toner, there was a greater than proportional increase retained at 16 and 64 mg/m^3, suggesting overloading. Clearance mechanisms were impaired at high exposures up to 90 days. Lungs had increased particle-laden macrophages with few in alveolar walls.
Muhle et al., 1990b. (report was limited) Identified in the Initial Literature Search	Test toner (carbon black pigmented acrylic polymer), polyvinyl chloride (PVC) powder, carbon black (type 'Printex 90')	Rats, inhalation exposure for up to 2 years, animals taken off study to evaluate at selected timepoints. Concentrations: Toner- 1, 4, 16.1, 63.2 mg/m^3; PVC, 3.3, 8.3, 20.2 mg/m^3 0 mg/m^3, carbon black, 9 mg/m^3, Diameter (μm), MMAD (μm) geometric SD, density: toner ~4, 4, 1.5, 1.15. PVC ~1.3, 1.3, 2.07, 1.3 carbon black ~0.014, 0.96, 2, 2	Particle clearance, measures of cytology (bronchoalveolar lavage fluid; BALF), lung histology; exposure resulted in retardation of alveolar clearance when retained mass reached a level of 0.5 mg per rat lung, with over 700 days of overloading (>10 mg per rat lung). After 24 months, an increase in polymorphonuclear cells was observed at 4 and 16 mg/m^3.
Muhle et al., 1991.	Test toner (contained 90% random copolymer CAS No.	Rats, whole-body inhalation exposure, 6	Both absolute and relative lung weights increased with increased retention of particles. Elevated toxicity measures in BALF were observed with increased

Identified in the Initial Literature Search	25213-39-2) and 10% high-purity carbon black CAS No. 7440- 44-0]; polymer composed of styrene and 1-butyl methacrylate (58:42)	hr/day, 5 days/wk for up to 24 months using a dry aerosol dispersion technique. Target concentrations 0, 1, 4, 16 mg/m^3 of toner, MMAD ~ 4.0 μm with GSD of 1.5	toner concentration. There was an exposure and time- dependent increase in the extent of particle-laden macrophages in lungs of toner-exposed rats. Toner increased primary lung tumors from 1 (adenoma) in the low dose to 3 tumors at the high concentration, without tumors identified in the mid concentration.
Oberdorster et al., 1992. Identified in the Initial Literature Search	^{141}Ce-labeled 3.3 μm diameter and 95 NB-labeled 10.3 μm diameter polystyrene microspheres were obtained as dry particles. Note: although useful in understanding the mode of action, the exposure following intratracheal administration is different from inhalation exposure.	Rats, intratracheal instillation of polystyrene particles; 40 μg and 100 μg of 3.3 μm particles and 10 and 100 μg of 10.3 μm particles—mixture of ^{141}Ce and ^{95}NB-polystrene particles-Diameter 3.3 and 10.3 μm; converting administered mass to volume; low-dose group received 2.2E7 μm^3, and the high-dose group received ~1.1E8 μm^3.	Overall particle clearance was AM (alveolar macrophage) mediated with translocation through the tracheobronchial (BL tree in the GI. The particle-associated radioactivity in the BL was the same whether it was large or small particles. There was no histological evidence for particle sequestration suggested by the aggregation of AM.

Table [SEQ Table * ARABIC]. Population: *In vitro* studies on polymer lung overload.

Reference	Polymer lung overload particles	Exposure/Comparator	Outcomes/Toxicities
Konczol et al., 2013.	Carbon-bearing particles (2-12 µm), rough surface covered with Fe_3O_4 submicron particles (30-200 nm); presence of rutile, cristobalite, perovskite.	Human epithelial A549 lung cells exposed to toner at 20-200 µg/cm^2 / 0 µg/cm^2 for up to 24 hours.	Endpoints included mitochondrial membrane depolarization, NF-kB binding activity, IL-6 and IL-8 levels, along with measures of cytotoxicity using water-soluble tetrazolium assay and neutral red uptake.
Wiemann et al., 2016. Identified in the Initial Literature Search	18 Inorganic nanomaterials, covering AlOOH, $BaSO_4$, CeO_2, Fe_2O_3, TiO_2, ZrO_2, and ZnO NMs, amorphous SiO_2 and graphite nanoplatelets, and two nanosized organic pigments. ZrO_2 and amorphous SiO_2 were tested without and with surface functionalization.	Rat NR8383 alveolar macrophages exposed to 22.5 to 180 µg/mL / 0 µg/mL Nanoparticle size (nm), surface areas BET (m^2/g), size in buffer, (nm) and concentration in buffer; ranged from 2 nm to <30 µm, 15 to 200 m^2/g, not detectable to 290 nm, not detectable to 1.3E8 particles/mL, respectively.	LDH, glucuronidase and tumor necrosis factor alpha, ROS/H_2O_2 measures were used to monitor responses after 16 hours of exposure. Based on particle surface area threshold, there were low *in vitro* effects compared to materials above the threshold (6000 mm^2/mL) that result in overloading and were considered active (2 of the 4 toxicity parameters). Overall, this assay was highly predictive of toxicity reported in short- term rat inhalation hazard potential for the same test substances.

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2. EXPERIMENTAL ANIMAL INHALATION STUDIES ON HMW POLYMERS

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
9000 Toner (styrene/butylmethacrylate random copolymer) MW: 70,000 Da Particle MMAD (GSD): 4.0 µm (1.5) Respirable fraction: 35%	SPF F344 rat, female (24/group)	Whole body inhalation (nose only for tracer exposure) 0, 10, 40 mg/m^3 aerosol 3 mo. (6 hr/d, 5 d/wk) 15 mo. recovery	10 mg/m^3 ↑ total protein in BALF ↓ tracer clearance rate (68-93% of control) 40 mg/m^3 ↑ PMNs, macrophages, LDH, β-glucuronidase, and total protein in BALF ↓ tracer clearance rate (20-63% of control)	Bellman 1992
ACUDYNE™ Shine Polymer (39-41% styrene/acrylates copolymer) and ACUDYNE ™ Bold Polymer MW: not reported Particle MMAD (GSD): not reported Respirable fraction: not reported	Rat (strain, sex, and group size not reported)	Nose only inhalation 10.8, 100 mg/mg^3 2 wk (frequency not reported	10.8 mg/m^3 None reported 100 mg/m^3 Slight irritant effects	Dow Chemical (undated) as cited in CIR 2014
ACUDYNE™ Shine Polymer (39-41% styrene/acrylates copolymer) and ACUDYNE ™ Bold	Rat (strain, sex, and group size not reported)	Nose only inhalation Concentrations not reported	NOAEL reported to be 8.3 mg/m^3 based on changes in lung and lymph nodes.	Dow Chemical (undated) as cited in CIR 2014

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
Polymer MW: not reported Particle MMAD (GSD): not reported Respirable fraction: not reported		13 wk (frequency not reported		
butyl acrylate/ methacrylic acid polymer MW: not reported Particle MMAD (GSD): not reported Respirable fraction: not reported	Rat (strain, sex, and group size not reported)	Inhalation (method not reported) 0, 1, 10, 30 mg/m^3 aerosol 3 mo. (frequency not reported) 6 wk recovery	1 mg/m^3 None reported 10 mg/m^3 None reported 30 mg/m^3 ↑ ("high") Incidence alveolar histiocytosis	Evans et al., 1998 [as cited in Norris and Tyler, 2000]
9000 Toner MW: 70,000 Da Particle MMAD (GSD): 4.0-4.1 µm (1.3) Respirable fraction: 34%	Syrian Golden Han:AURA hamster, male and female, (41 M and 24 F/group for main study)	Whole body inhalation 0, 4, 16, 64 mg/m^3 aerosol 90 d (6 hr/d, 5 d/wk) Up to 100 d recovery	4 mg/m^3 ↑ absolute and/or relative lung weight ↑ incidence accumulation of particle-laden alveolar macrophages 16 mg/m^3 ↑ absolute and/or relative lung weight ↑ incidence lung/LALN histopathology ("slight appearance of particles" in LALN; accumulation of particle-laden alveolar macrophages; very slight septal thickening due to hypercellularity and interstitial inflammatory cell infiltrate) ↑ grey/black areas of lungs (retained test material) 64 mg/m^3 ↑ absolute and/or relative lung weight ↑ incidence lung/LALN histopathology ("slight appearance of	Fraunhofer Institute, 1988 (Unpublished report) There were 19 unscheduled sacrifices unrelated to treatment; in addition, 30% of the animals (mostly males) exhibited wet tail disease

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
			particles" in LALN; accumulation of particle-laden alveolar macrophages; very slight septal thickening due to hypercellularity and interstitial inflammatory cell infiltrate) ↑ grey/black areas of lungs (retained test material), discolored LALN	
Toner A (styrene/butylmethacrylate random copolymer) MW: Not reported Particle MMAD (GSD): 4.0 µm (1.5) Respirable fraction: 35%	F344/CrlBR rat, female, (58-66/group)	Whole body inhalation 0, 4, 16, 64 mg/m^3 aerosol 3 mo. (6 hr/d, 5 d/wk) Up to 6 mo. recovery	4 mg/m^3 ↑ incidence slight to moderate accumulation particle-laden macrophages 16 mg/m^3 ↑ incidence very slight interstitial fibrosis in lungs ↑ incidence slight to moderate accumulation particle-laden macrophages in lungs ↑ incidence slight interstitial inflammatory cell infiltration in lungs ↓ tracer clearance rate (half-time 1.3X to 1.7X control) 64 mg/m^3 ↑ LDH, β-glucuronidase, total protein, hydroxyproline, and PMN count in BALF ↑ absolute wet and dry lung weights, lymph node weights ↑ very slight interstitial fibrosis in lungs ↑ slight to moderate accumulation particle-laden macrophages in lungs ↑ slight interstitial inflammatory cell infiltration ↑ alveolar PMN infiltration ↑ focal/multifocal alveolar type-II cell hyperplasia ↓ tracer clearance rate (half-time 2.1X to 8.8X control) ↑ grey/black areas of lungs (retained test material), discolored LALN	Fraunhofer Institute, 1991a. (Unpublished report) There were 17 unscheduled sacrifices unrelated to treatment.
Toner B (styrene/ butadiene random copolymer) MW: not reported Particle MMAD (GSD): 4.0-	F344/CrlBR rat, female (50/group for main study, 10/group for clearance)	Whole body inhalation 0, 1, 4, 16, or 64 mg/m^3 aerosol	1 mg/m^3 None reported 4 mg/m^3 None reported 16 mg/m^3	Fraunhofer Institute, 1991b. (Unpublished report) There were 3 unscheduled sacrifices unrelated

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
4.2 µm (1.5-1.8) Respirable fraction: 35.4-37.2%		3 mo. (6 hr/d, 5 d/wk) Up to 6 mo. recovery	↑ grey/black areas of lungs (retained test material) <u>64 mg/m^3</u> ↑ LDH, β-glucuronidase, and PMNs in BALF ↑ enlargement of LALN ↑ very slight to slight focal/multifocal alveolar type II cell hyperplasia ↑ very slight to slight focal/multifocal interstitial inflammatory cell infiltration in lungs ↑ very slight to slight interstitial fibrosis in lungs ↑ slight to moderate particle deposition in LALN ↑ slight to moderate lymphoid hyperplasia in LALN ↓ tracer clearance rate (half-time 1.2X to 2.2X control) ↑ grey/black areas of lungs (retained test material), discolored LALN	to treatment.
9000 Toner (styrene/butylmethacrylate random copolymer) MW: 70,000 Da Particle MMAD (GSD): 4.0 µm (1.6-1.8) Respirable fraction: 36.5-37.7%	Syrian Golden Han:AURA hamster, male and female, (50/group)	Whole body inhalation 0, 1.5, 6, or 24 mg/m^3 (mo. 1-5); 0, 4, 16, or 64 mg/m^3 (mo. 6-18) aerosol 18 mo. (6 hr/d, 5 d/wk) 3-5 mo. recovery	<u>1.5/4.0 mg/m^3</u> ↑ bronchiolar/alveolar hyperplasia in males ↑ accumulation particle-laden macrophages ↑ interstitial inflammatory cell infiltration in males ↑ lymphatic hyperplasia in LALN in males ↑ particle deposits in LALN <u>6/16.0 mg/m^3</u> ↑ interstitial fibrosis ↑ bronchiolar/alveolar hyperplasia ↑ accumulation particle-laden macrophages ↑ alveolar PMN infiltration ↑ interstitial inflammatory cell infiltration ↑ lymphatic hyperplasia in LALN ↑ particle deposits in LALN <u>24/64 mg/m3</u> ↓ % lymphocytes; ↑% and absolute count neutrophils in blood ↑ absolute and relative lung weight ↑ total cell number, PMNs, macrophages, LDH, β-glucuronidase, total protein, and hydroxyproline in BALF ↑ interstitial fibrosis	Fraunhofer Institute, 1991c (Unpublished report)

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
			↑ bronchiolar/alveolar hyperplasia ↑ accumulation particle-laden macrophages ↑ alveolar PMN infiltration ↑ interstitial inflammatory cell infiltration ↑ lymphatic hyperplasia in LALN ↑ particle deposits in LALN ↓ tracer clearance rate (half-time 1.7 to 3.1X control) in males	
Ultrafine Kevlar Aramid synthetic fibrils MW: not reported Particle MMAD (GSD): <2 µm (GSD not reported) Respirable fraction: >70%	Crl:CD(SD)BR rat, male and female (100/sex/group)	Whole body inhalation 0, 0.08, 0.32, 0.63, or 2.23 mg/m^3 (0, 2.5, 25, 100, or 400 fibers/cc) 24 mo. (6 hr/d, 5 d/wk) 12 mo. recovery (2.23 mg/m^3 group only)	0.08 mg/m^3 ↑ slight dust cell (macrophage) response 0.32 mg/m^3 ↑ dust cell (macrophage) response ↑ foamy macrophage response ↑ hyperplasia of type II pneumocytes ↑ collagenized fibrosis ↑ alveolar bronchiolization 0.63 mg/m^3 ↑ lung weight ↑ dust cell (macrophage) response ↑ foamy macrophage response ↑ hyperplasia of type II pneumocytes ↑ collagenized fibrosis ↑ alveolar bronchiolization ↑ cholesterol granuloma in females 2.23 mg/m^3 ↑ mortality due to obliterative bronchiolitis (29 M and 14 F) ↑ lung weight ↑ dust cell (macrophage) response ↑ foamy macrophage response ↑ hyperplasia of type II pneumocyte ↑ collagenized fibrosis ↑ alveolar bronchiolization ↑ cholesterol granuloma in females ↑ centriacinar emphysema ↑ keratinized cystic squamous cell carcinoma in females (6/56)	Lee et al. 1988

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
Polyvinyl chloride (PVC) powder MW: Not reported Particle MMAD (GSD): 1.3 µm (2.07) Respirable fraction: not reported	Rat, female (strain not reported); group sizes not reported	Inhalation (method not reported) 0, 3.3, 8.3 or 20.2 mg/m^3 7 mo. (25 hr/wk) 15-100 d recovery	3.3 mg/m^3 ↓ tracer clearance rate (mean half-time 1.2X control) 8.3 mg/m^3 ↓ tracer clearance rate (mean half-time 2.1X control) 20.2 mg/m^3 ↓ tracer clearance rate (mean half-time 3.2X control)	Muhle et al., 1990b (21: 374)
9000 Toner (styrene/butylmethacrylate random copolymer) MW: 70,000 Da Particle MMAD (GSD): 4.0 µm (1.5) Respirable fraction: 35%	SPF F344 rat, male and female (56-74/sex/group)	Whole body inhalation (nose only for tracer exposure) 0, 1, 4, 16 or 64 mg/m^3 aerosol 3 mo. (6 hr/d, 5 d/wk) 3 mo. recovery	1 mg/m^3 None reported 4 mg/m^3 None reported 16 mg/m^3 ↑ tachypnea ↑ relative lung weight in males ↑ slight LALN enlargement ↑ lung histopathology (particle-laden macrophages, few particles found in alveolar walls; slight degree of thickening of the alveolar structure due to hypertrophy and hyperplasia of Type II cells and accumulation of a few interstitial cells) 64 mg/m^3 ↑ tachypnea ↑ absolute and relative lung weights ↑ slight LALN enlargement ↑ lung histopathology (particle-laden macrophages, few particles found in alveolar walls; slight degree of thickening of the alveolar structure due to hypertrophy and hyperplasia of Type II cells and accumulation of a few interstitial cells)	Muhle et al., 1990a (2: 341)
9000 Toner (styrene/butylmethacrylate	SPF F344 rats, male and female	Whole body inhalation	1 mg/m^3 ↑ occasional particle-laden macrophages	Muhle et al., 1991 (17: 280); Bellmann

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
random copolymer) MW: 70,000 Da Particle MMAD (GSD): 4.0 µm (1.5) Respirable fraction: 35%	(100/sex/group in main study)	(nose only for tracer exposure) 0, 1, 4, or 16 mg/m^3 aerosol 24 mo. (6 hr/d, 5 d/wk) Up to 2 mo. recovery	4 mg/m^3 ↑ PMN and lymphocytes in BALF ↑ particle-laden macrophages ↑ foamy macrophage accumulation, very slight ↑ pulmonary fibrosis, minimal to mild ↓ tracer clearance rate (mean half-time 1.2X – 2.3X control) 16 mg/m^3 ↓ lung volume and compliance ↑ absolute and relative lung weights ↓ macrophages, ↑ PMN, lymphocytes, LDH, β-glucuronidase and protein in BALF ↑ particle-laden macrophages ↑ foamy macrophage accumulation, slight ↑ bronchioalveolar hyperplasia, slight to moderate ↑ alveolar squamous cell metaplasia in some females ↑ cholesterol granulomas (occasional) ↑ alveolar lipoproteinosis, very slight to slight ↑ pulmonary fibrosis, mild to moderate ↑ lymphoid hyperplasia of LALN ↓ tracer clearance rate (mean half-time 2.1X -6.6X control)	et al., 1991; Muhle et al., 1989; Heinrich et al., 1989
ADR (acrylic latex consisting of ethyl acrylate, methacrylic acid, methyl methacrylate, acrylic acid polymer) MW: not reported Particle MMAD (GSD): 2.64-3.09 µm (3.54-3.90) Respirable fraction: not reported	Sprague-Dawley rat, male and female (10-15/sex/group)	Whole body inhalation 0, 30, 100 or 300 mg/m^3 aerosol 3 mo. (2 hr/d, 5 d/wk) 6 wk recovery (5 females only)	30 mg/m^3 None reported 100 mg/m^3 ↑ alveolar histiocytosis ↑ lymphadenitis in mediastinal lymph nodes ↑ interstitial pneumonitis in recovery females 300 mg/m^3 ↑ absolute and relative lung weights ↑ alveolar histiocytosis ↑ lymphadenitis in mediastinal lymph nodes ↑ intra-alveolar cellular debris in recovery females ↑ interstitial pneumonitis in recovery females	Norris and Tyler, 2000

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
HMDI-based polyurethane/ polyurea polymer MW: >20,000 Da Particle MMAD (GSD): 1.00-1.54 µm (1.86-1.94) Respirable fraction: 4.3-6.1% (modeled)	SPF Wistar rat, male and female (10-15F and 22M/group)	Nose only inhalation 0, 5, 26 or 107 mg/m^3 13 wk (6 hr/d, 5 d/wk) 4 wk recovery	5 mg/m^3 None reported 26 mg/m^3 ↑ absolute wet lung weight ↑ total cell count, MCV, alveolar macrophage and PMN counts, total protein, LDH and GGT in BALF ↑ incidence mucus and/or cells in the trachea and pulmonary airways; enlarged and/or foamy macrophages in lung; hypercellularity of the bronchiolo-alveolar junction; polymer/debris-laden macrophages in LALNs 107 mg/m3 ↑ absolute wet lung weight ↑ total cell count, MCV, alveolar macrophage and PMN counts, neutrophil count, total protein, LDH and GGT in BALF ↑ incidence mucus and/or cells in the trachea and pulmonary airways; enlarged and/or foamy macrophages in lung; hypercellularity of the bronchiolo-alveolar junction; polymer/debris-laden macrophages in LALNs	Pauluhn, 2014
HMDI-based polyurethane/ polyurea polymer MW: >20,000 Da Particle MMAD (GSD): 0.9-1.4 µm (2.2-2.5) Respirable fraction: not reported	SPF Wistar rat, male (6-12/group)	Nose only inhalation 0, 5, 22, or 121 mg/m^3 2 wk (6 hr/d, 5 d/wk) 2 wk recovery	5 mg/m^3 None reported 22 mg/m^3 ↑ MCV in BALF Minimal changes in alveolar macrophage morphology 121 mg/m^3 ↑ total cell count, MCV, alveolar macrophage and PMN counts, total protein, LDH, and GGT in BALF ↑ absolute lung wet weight ↑ incidence hyperplastic and hypertrophic alveolar macrophages (alveolar histiocytosis) containing foamy-brownish cytoplasmatic inclusions ↑ incidence hypercellularity/epithelial thickening at the bronchiolo-alveolar junction with inflammatory infiltrates, increased numbers of alveolar macrophages, and focal septal thickening	Pauluhn, 2014

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference
HMDI-based polyurethane/ polyurea polymer MW: >20,000 Da Particle MMAD (GSD): not reported Respirable fraction: not reported	SPF Wistar rat, male (18/group)	Nose only inhalation 0, 57, or 979 mg/m^3 6 hr 1 wk recovery	57 mg/m^3 ↑ PMN count and GGT in BALF 979 mg/m^3 ↓ body weight ↑ frequency of transient respiratory effects and hypothermia ↑ absolute lung wet weight ↑ total cell count, MCV, alveolar macrophage count, PMN count, total protein, LDH, and GGT in BALF	Pauluhn, 2014
Acrylates copolymer (n-butyl acrylate, methyl methacrylate, and methacrylic acid) MW not reported Particle MMAD (GSD): 2.4-2.5 µm (GSD not reported) Respirable fraction: not reported	Crl:CD(SD)BR rat, male and female (15/sex/group)	Whole body inhalation 0, 1, 10, 30 mg/m^3 (as formulation) or 0.185, 1.67, or 4.94 mg/m^3 (polymer) 13 wk (6 hr/d, 7 d/wk) 4 wk recovery	1/0.85 mg/m^3 None reported 10/1.67 mg/m^3 None reported 30/4.94 mg/m^3 ↑ lung weight ↑ alveolar histiocytosis with focal macrophage accumulation in alveolar spaces	WIL Research Laboratories, Inc., 1997 (as cited in CIR, 2002)

↑ = statistically or biologically significant increase; ↓= statistically or biologically significant decrease; LALN = lung-associated lymph nodes; BALF = broncho-alveolar lavage fluid; LDH – lactate dehydrogenase; GGT = γ glutamyltransferase; MCV = mean cellular volume of lavageable cells; PMN = polymorphonuclear neutrophils

[a] TEST MATERIAL DETAILS:
9000 Toner: 9000-type xerographic toner material composed of about 90% 58:42 styrene/butylmethacrylate random copolymer (CAS no. 25213-39-2) and 10% high-purity furnace-type carbon black (CAS no. 7440-44-0)

Toner A; 1075 Toner Fines; composition corresponds to 1075 xerographic toner. >90% random copolymer (CASRN 25213-39-2); 5-10% high purity furnace black (CASRN 1333-86-4); ~2% quaternary ammonium salt cetyl pyridinium chloride (CASRN 123-03-5)

Toner B; S090 Toner Fines; composition corresponds to 5090 xerographic toner. 75-85% random copolymer (styrene/butadiene; CASRN 9003-55-8); <5%

Table [SEQ Table * ARABIC]. Inhalation studies of lung overload from HMW polymers in laboratory animals.

Test Material[a]	Animals	Exposure and Recovery	Lung effects	Reference

high purity furnace black (CASRN 1333-86-4); 15-20% iron oxide (CASRN 1309-37-1); <2% quaternary ammonium salts (CASRNs 3843-16-1 and 123312-54-9)

Aqueous dispersion resin (ADR) is a water-based acrylate copolymer supplied by Amerchol Corporation (lot 10-19-92; Edison, NJ) containing 26% of an acrylic latex consisting of ethyl acrylate, methacrylic acid, methyl methacrylate, acrylic acid polymer (CAS RN 25053-63-8), formulated in 73% water neutralized to pH 7 with 1% salts and surfactants

HDMI-based polyurethane-polyurea polymer. Poorly soluble, slowly biodegradable linear anionic hexamethylene diisocyanate monomer-based polyurethane-polyurea HMW polymer of >20,000 Da incorporating both hydrophilic and hydrophobic segments. When dispersed in water, the insoluble content of dispersion was approximately 30%.

Acrylates copolymer (n-butyl acrylate, methyl methacrylate, and methacrylic acid). Vehicle and polymer formulation had 69% ethanol (16.2% solids by wt, viscosity 16 cPs, and pH 8.4). Contained monomer levels of 5 ppm n-butyl acrylate, 33 pm methyl methacrylate, and 15.7 methacrylic acid.

3. BENCHMARK DOSE (BMD) MODELING OUTPUTS

EPA's BMD software (BMDS, 3.1.1) was used for dose-response modeling of dichotomous data. All dichotomous models in the software were considered. A benchmark response (BMR) of 10% extra risk was employed, and model fit was evaluated using the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals at doses near the BMR, and visual assessment of the model fit as displayed graphically. The BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen from among all models providing adequate fit.

Muhle et al. 1991; Bellmann et al., 1991; Muhle et al., 1989; Heinrich et al., 1989

The incidence of pulmonary fibrosis (all severity levels, minimal to moderate) in rats exposed to 9000 type print toner for 2 years (6 hours/day, 5 days/week) was subjected to BMD modeling. The modeled data are shown in [REF _Ref46549694 \h * MERGEFORMAT] below.

Table [SEQ Table * ARABIC]. Incidence of pulmonary fibrosis in rats exposed to 9000 print toner (21-26-month sacrifices).

Exposure concentration (mg/m^3)	Number exposed[a]	% Affected	Number affected
0	90	1.2	1
1	90	0	0
4	90	21.6	19
16	90	92.1	83

[a] Number per group was reported as "about 90 animals/exposure group". Number affected was calculated as % affected (summed across severity groups) x 90 and rounded to nearest integer.

Source: Muhle et al. 1991

Models providing adequate fit (χ^2 $p > 0.1$) to the fibrosis incidence data included gamma, log-logistic, multistage (2- and 3-degree), and log-probit. Among these, the log-probit model had the lowest AIC and was selected. The BMC and BMCL predicted by the log-probit model were 3.0 and 2.5 mg/m^3, respectively. BMD model output and graphical display of the data fit for the log-probit model are shown below.

A. BMD Model Output for Selected Model (Log-Probit) for Pulmonary Fibrosis

Frequentist Log-Probit Unrestricted Option Set #1

User Input

Info	
Model	frequentist Log-Probit v1.1
Dataset Name	Muhle1991_toner_fibrosis_2yr
User notes	[Add user notes here]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Incidence]
Total # of Observations	4

Model Results

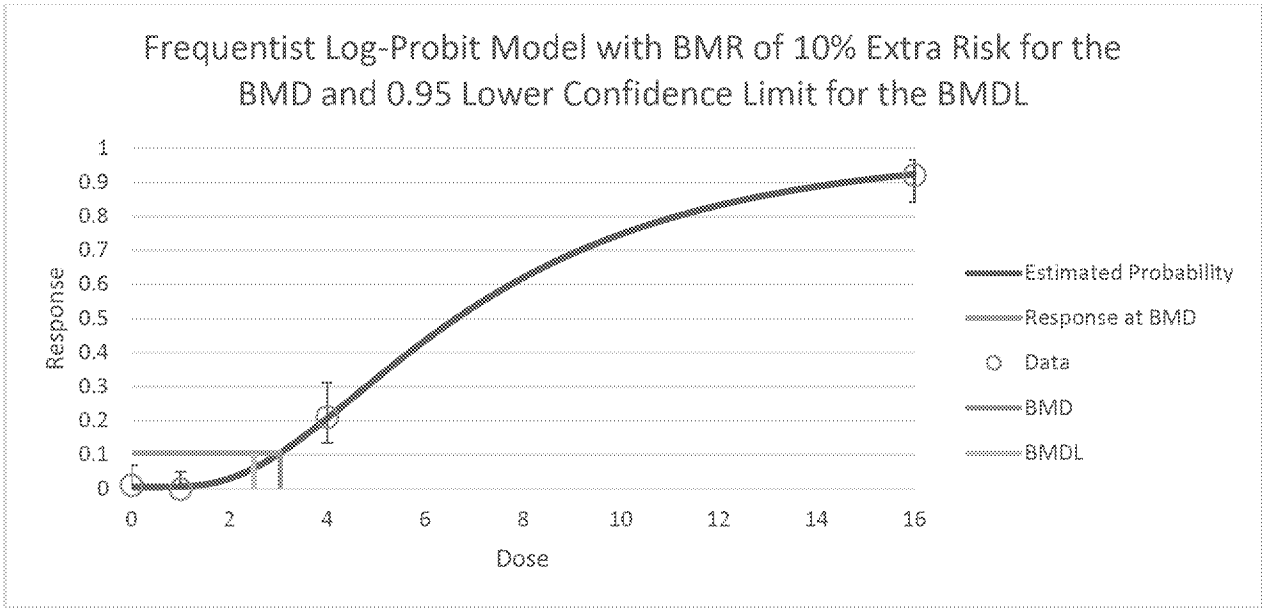
Benchmark Dose	
BMD	3.03602163
BMDL	2.495470955
BMDU	3.583395138
AIC	160.5429675
P-value	0.294321824
D.O.F.	1
Chi^2	1.099746133

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.005598734
a	-3.09242313
b	1.630610825

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.005598734	0.503886102	1	90	0.700865
1	0.006585825	0.59272426	0	90	-0.772434
4	0.207191742	18.64725679	19	90	0.0917418
16	0.923867598	83.14808379	83	90	-0.058857

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value

Full Model	-76.48022106	4	-	-	-
Fitted Model	-77.27148375	3	1.58252536	1	0.2083973
Reduced Model	-215.5078117	1	278.055181	3	<0.0001



Lee et al. 1988

Several lung lesions were significantly increased by 24-month exposure to Kevlar fibrils at the LOAEC mass/volume concentration of 0.32 mg/m^3 (Lee et al., 1988). Incidences of all lesions affected at the LOAEC are shown in [REF _Ref46550170 \h * MERGEFORMAT] below. Among the five lesion types increased at the LOAEC, two were selected for BMD modeling (shown in bold in [REF _Ref46550170 \h * MERGEFORMAT]): foamy macrophage response and alveolar bronchiolarization. The remaining three lesions exhibited "all or none" dose-response relationships that are not amenable to BMD modeling.

Table [SEQ Table * ARABIC]. Incidence of pulmonary pathology[a] in rats exposed to Kevlar fibrils for 24 months.

Exposure concentration (mg/m^3)	Number exposed	Dust cell (macrophage) response	Foamy macrophage response	Type II pneumocyte hyperplasia	Fibrosis, collagenized	Alveolar bronch-iolarization
Male						
0	69	0	**7**	0	0	**0**
0.08	69	1	**2**	1	0	**0**
0.32	67	65	**21**	65	67	**37**
0.63	68	67	**47**	67	67	**48**
2.32	36	32	**18**	32	35	**16**
Female						
0	68	0	**4**	0	0	**0**
0.08	64	0	**3**	0	0	**1**
0.32	65	63	**20**	63	57	**51**
0.63	69	68	**65**	68	65	**68**
2.32	56	54	**51**	54	54	**52**

[a] Bolded column indicate data subjected to BMD modeling

Source: Lee et al., 1988

[REF _Ref46550526 \h * MERGEFORMAT] presents the BMD modeling results for pulmonary pathology in rats exposed to Kevlar fibrils. As the Table shows, no model fit was achieved when all dose groups were included in modeling of incidences (either lesion) in males. With the high dose group omitted, the 2-degree multistage model was the only model providing adequate fit to the incidences of foamy macrophages in males; this model provided BMC and BMCL estimates of 0.19 and 0.15 mg/m^3, respectively. For alveolar bronchiolarization in males, no model fit was achieved with the high dose group omitted; with the two highest dose groups omitted, all but the 1-degree multistage model provided adequate fit, and the dichotomous Hill model had the lowest AIC. The BMC and BMCL predicted by this model were 0.28 and 0.09 mg/m^3, respectively.

For incidences of both foamy macrophages and alveolar bronchiolarization in female rats, the dichotomous Hill model was the only model providing adequate fit to the full datasets. This model yielded BMC and BMCL estimates of 0.28 and 0.24 mg/m^3 for foamy macrophages and 0.13 and 0.10 mg/m^3 for alveolar bronchiolarization in female rats.

Table [SEQ Table * ARABIC]. BMD Modeling Results for Pulmonary Pathology in Rats Exposed to Kevlar Fibrils for 2 years.

Sex - Lung Lesion Type	Dataset	Selected model	BMC (mg/m^3)	BMCL (mg/m^3)
Male – Foamy macrophages	All	No model fit		
	HDD	Multistage 2 degree	0.19	0.15
Male – Alveolar bronchiolarization	All	No model fit		
	HDD	No model fit		
	2HDD	Dichotomous Hill	0.28	0.09
Female – Foamy macrophages	All	Dichotomous Hill	0.28	0.24
Female – Alveolar bronchiolarization	All	Dichotomous Hill	0.13	0.10
BMC = benchmark concentration; BMCL = lower confidence limit on benchmark concentration; HDD = highest dose group omitted; 2HDD = 2 highest dose groups omitted.				

The lowest BMCL shown in the table is 0.09 mg/m^3; however, because this BMCL was obtained only by dropping two of the four exposure groups, and was very close to the BMCL of 0.1 mg/m^3 obtained by modeling alveolar bronchiolarization in females using all exposure groups, the latter was selected as the best POD for this study. BMD model output and graphical display of the female alveolar bronchiolarization data fit for the dichotomous Hill model are shown below.

B. BMD Model Output for Selected Model (Dichotomous Hill) for Female Alveolar Bronchiolarization

Frequentist Dichotomous Hill Unrestricted Option Set #1

User Input

Info	
Model	frequentist Dichotomous Hill v1.1
Dataset Name	Lee1988_synfibers_bronchiol_2yr_females
User notes	[Add user notes here]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Dose]
Independent Variable	[Incidence]
Total # of Observations	5

Model Results

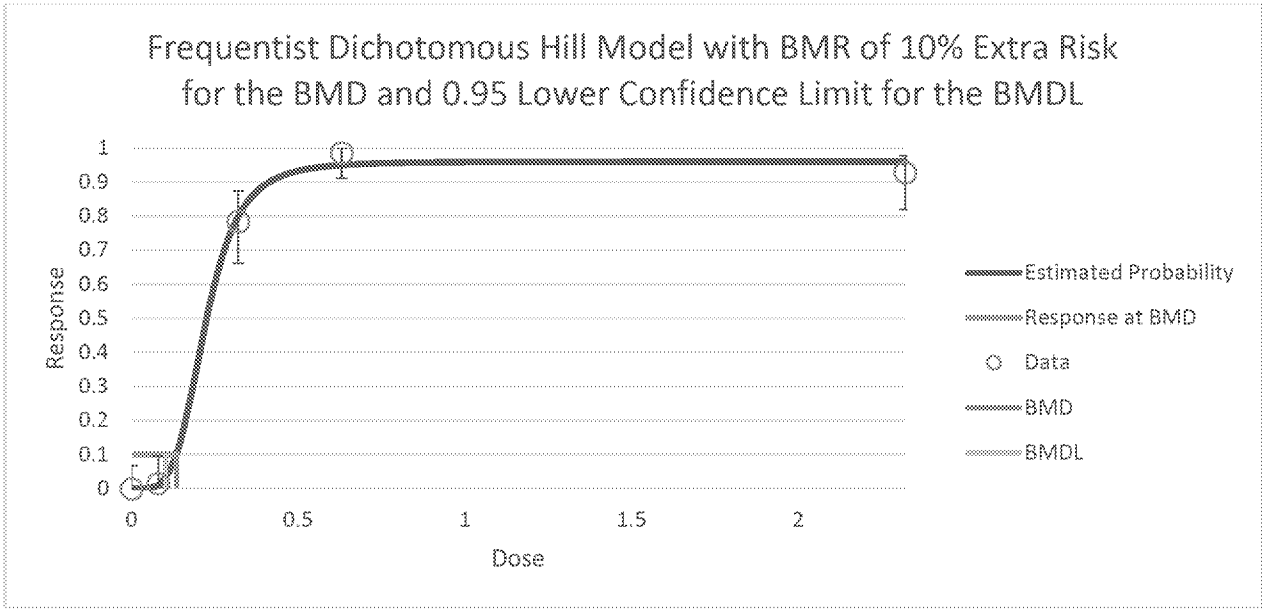
Benchmark Dose	
BMD	0.134448091
BMDL	0.102215165
BMDU	0.174500488
AIC	127.1745156
P-value	0.176399296
D.O.F.	2

Chi^2	3.470010254

Model Parameters	
# of Parameters	4
Variable	Estimate
g	Bounded
v	0.960289295
a	6.528285835
b	4.325966045

Goodness of Fit					
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	1.03564E-06	0	68	-0.001018
0.08	0.011670656	0.746921978	1	64	0.2945547
0.32	0.798861796	51.92601671	51	65	-0.286536
0.63	0.950042444	65.55292861	68	69	1.3522282
2.32	0.960252474	53.77413855	52	56	-1.213517

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-58.65296117	5	-	-	-
Fitted Model	-60.58725782	3	3.8685933	2	0.1445259
Reduced Model	-222.4412535	1	327.576585	4	<0.0001



4. MPPD Modeling Outputs

The predictions for Muhle *et al.* (1990) shown in [REF _Ref46769100 \h], below, are specific to those experimental parameters only, so we conducted additional simulations to impart appreciation of why they should be conducted with exact particle exposure characteristics, experimental conditions (concentration, duration), and species parameters for any polymer undergoing evaluation.

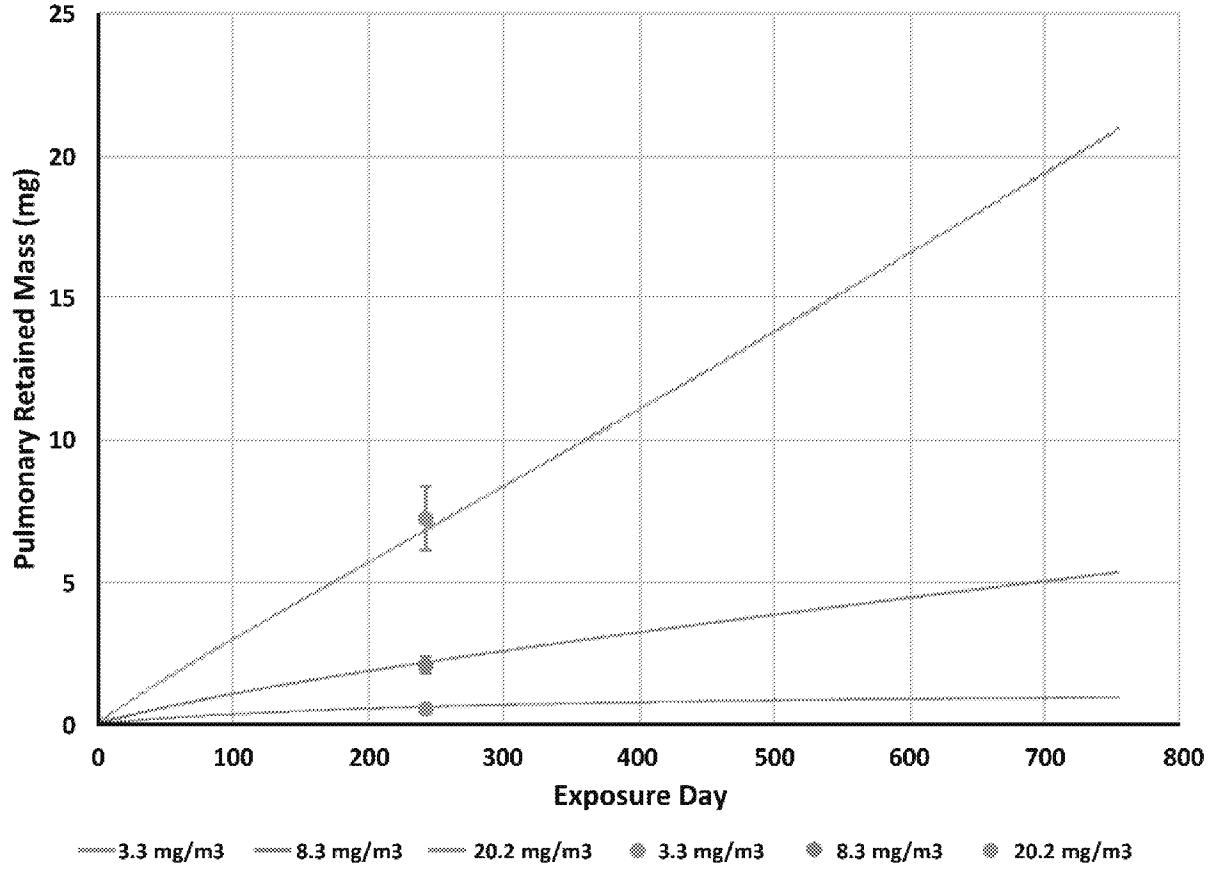


Figure [SEQ Figure * ARABIC]. MPPD predictions for retained PU mass in F344 rats under the exposure conditions for the Muhle *et al.* (1990) study**.** Simulations were performed to characterize the 8-month study with a particle MMAD size of 1.3 μm, a GSD of 2.07, and a density of 1.3 g/cm^3 for three concentrations (3.3, 8.3, and 20.2 mg/m^3). Experimental data for PU burdens are shown as solid circles with standard deviation and the predictions as solid lines for different concentrations.

Additional simulations were conducted at the same three exposure concentrations as Muhle *et al.* (1990), but the following three key input parameters were varied and bounded based on the rationale provide below.

1) MMAD: 0.1, 2.5, and 10 μm. This represents a range of particle sizes covering different dominant deposition mechanisms across species and covers size range of particles for which overload was demonstrated in Muhle *et al.* (1990). [REF _Ref46769370 \h *

MERGEFORMAT] illustrates the impact of predicted retained PU mass (mg) for simulations for particles sizes of MMAD at 0.1, 2.5, and 10 μm.

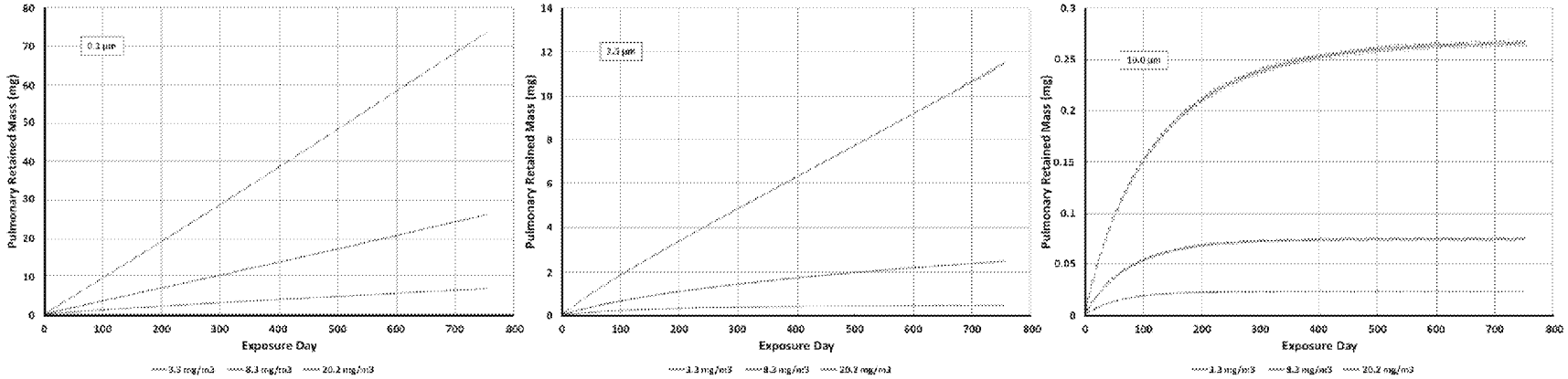


Figure [SEQ Figure * ARABIC]. Impact of particle size on predicted inhaled retained mass burden in PU region of F344 rats. Simulations were performed under the same exposure conditions as for the Muhle *et al*. (1990) study with an exposure of 5 h /d and 5 d/w with a particle GSD of 2.07 and density of 1.3 g/cm^3; and at the same concentrations. The three panels show predicted retained PU mass (mg) for an MMAD of 0.1 µm (left), 2.5 µm (middle), and 10.0 µm (right); note the y-axis is different for each.

At the largest particle size, overload is not predicted to be achieved in the rat. For the particle size with an MMAD of 2.5 μm, slightly larger than the MMAD of 1.3 μm in the Muhle *et al.* (1990) study, overload is only evident at the highest exposure concentration; whereas for the MMAD of 0.1 μm, predictions indicate overload would occur in the rats at all three exposure concentrations. There are also associated substantial differences in the predicted mass with a 400% increase in PU burden at the lowest particle size; whereas at the larger particles sizes with an MMAD of 2.5 and 10 μm, predictions for retained PU mass are decreased by 50-60% and two orders of magnitude (99%), respectively.

2) GSD: 1, 2.07, and 3 with an MMAD of 3.5 μm. If an exposure aerosol has a GSD greater than 3, it calls into question the quality of the control on exposure generation and characterization. This range includes the GSD of 2.07 used in the Muhle *et al.* (1990) study. We chose a particle size of 3.5 μm with the same density of the PVC particles in the Muhle *et al.* (1990) study to illustrate how filtering due to impaction mechanisms for this particle size in the extrathoracic (ET) region of the respiratory tract influences what penetrates to the lower respiratory tract for deposition and subsequent clearance. A large GSD near that size range can substantively impact retained PU mass results. [REF _Ref46769955 \h * MERGEFORMAT] illustrates the impact of variation in the GSD for an aerosol with particle size MMAD of 3.5 μm. At the larger GSD, there is a 15% predicted decrease in the retained PU mass but when the aerosol is monodisperse with a GSD of 1.0, there is a 50% increase in the predicted retained PU mass and overload most evident at the highest concentration. The decrease in predicted retained PU mass at the larger GSD illustrates the filtering effect in the ET region. We also ran simulations with an MMAD of 1.3 μm as in the Muhle *et al.* (1990) study for a GSD of 1.0 and 3.0.

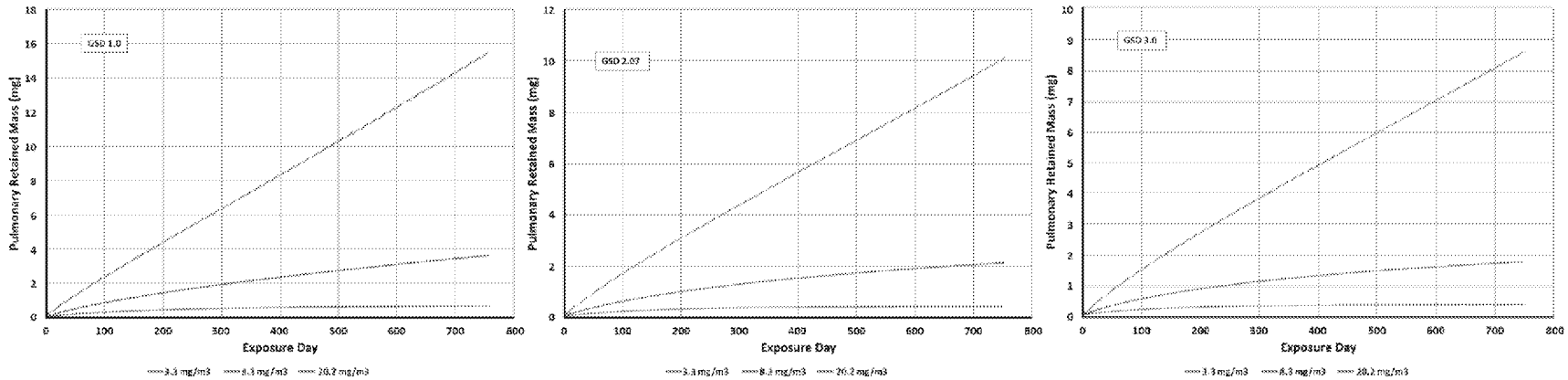


Figure [SEQ Figure * ARABIC]. Impact of geometric standard deviation (GSD) on predicted inhaled retained mass burden in PU region of F344 rats for a particle exposure with an MMAD of 3.5 μm. Simulations were performed under the same exposure conditions (5 h/d and 5 d/w) as for the Muhle *et al*. (1990) study, including a density of 1.3 g/cm^3 and at the same concentrations. The three panels show predicted retained PU mass (mg) for a GSD of 1.0 (left), 2.08 (middle), and 3.0 (right); note the y-axis is different for each. The middle GSD is the same as that in the Muhle *et al*. (1990) study.

For this particle size, a 5% decrease is instead predicted at a GSD of 1.0 and an increase of 5% at the larger GSD of 3.0. These simulations illustrate and reinforce the need for exposure specific data for determining these input parameters.

3) Density: 0.85 and 2.0 g/cm^3. This span of density between 0.85 and 2.0 g/cm^3 covers the range of density based on values for plastic polymers provided in Lambert and Wagner (2017). Simulations used all other input parameters the same as in the Muhle *et al.* (1990) study. [REF _Ref46769919 \h * MERGEFORMAT] shows predictions for each of these density values at the three concentrations. The predicted retained PU burdens in rats are 5-10% less than at the density of 1.3 g/cm^3 shown in Figure 2, whereas a 10% increase in retained PU burden is predicted for the higher density. Predicted overload is approximately the same for each.

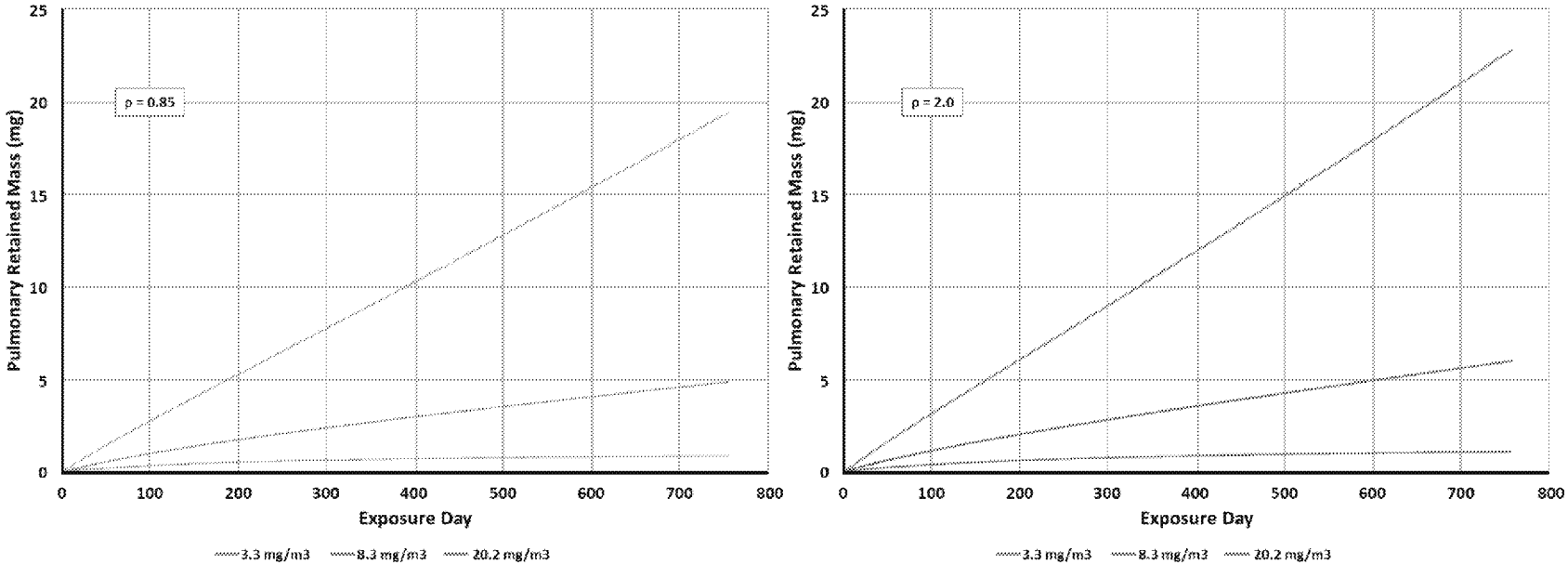


Figure [SEQ Figure * ARABIC]. Impact of particle density (ρ) on predicted inhaled retained mass burden in PU region of F344 rats. Simulations were performed under the same exposure conditions as for the Muhle *et al*. (1990) study with an exposure of 5 h /d and 5 d/w with a particle MMAD of 1.3 μm and GSD of 2.07; and at the same concentrations. The panel on the left is for ρ = 0.85 g/cm^3 and the right for ρ = 2.0 g/cm^3, values which bracket available data for density of plastic polymers.

While this set of simulations does not provide a full evaluation of the sensitivity matrix for these parameters since we varied only one at a time and an actual scenario might simultaneously vary all three, the simulations do impart appreciation for potential variability and thus, impact on inferences. The simulations for the rat studies allow evaluation of whether overload would be achieved or not with a specific exposure (*i.e.*, concentration, regimen / duration, MMAD, GSD and density) to inform inferences based on observed toxicity, and are also the basis for the simulations used to calculate human equivalent concentrations (HECs), as discussed below.

For extrapolation of the predicted rat retained mass to an HEC, human simulations were conducted for adult males with a V_T of 0.992 L and a breathing frequency of 21 bpm, or with 1.364 L and 33 bpm. These ventilatory values are from the ICRP (1994) and represent ventilation associated with activity levels of either light exercise or heavy exercise for adult males. It should be noted that this combination of V_T and bpm for the light exercise ventilation input parameters are equivalent to the default minute ventilation value (V_E) used by EPA of 1.25 m^3/hr. An occupational exposure duration of 40 years was simulated for the human predictions of retained mass in the PU region.

The dose metric used to operationally derive the HEC is the PU retained mass (mg) normalized to the PU surface area (SA) in cm^2 according to the established US EPA methods (US EPA, 1994). The MPPD model estimates a human pulmonary surface area of 66.3 m^2 for an 80 kg adult male. Simulations are performed iteratively to arrive at a human equivalent exposure concentration (HEC) that achieves the same internal dose metric (PU mass / PU SA) in humans as was achieved in rats under the experimental conditions, in this case using the Muhle et al. (1990) conditions as described previously. As was shown in [REF _Ref46769100 \h * MERGEFORMAT], the predicted retained mass in the PU region corresponds well with the observed experimental data. The last two rows of the tables demonstrate the difference in HEC value due to variation in ventilatory parameters associated with either light or heavy activity. The human ventilation rate used in the simulations to calculate the HEC has direct impact on the relative contribution of deposition mechanisms and interacts with particle size especially as presented in [REF _Ref46770696 \h] and [REF _Ref46770706 \h]. [REF _Ref46770696 \h] shows the same simulation using an MMAD of 0.1 μm, whereas [REF _Ref46770706 \h] was run for a particle MMAD of 10.0 μm.

Table [SEQ Table * ARABIC]. MPPD predictions and HEC calculations for a hypothetical PVC exposure to F344 Rats with a particle MMAD of 0.1 μm, GSD of 2.07, and density of 1.3 gm / cm^3.

Exposure Concentration (mg/m^3)	3.3	8.3	20.2
Predicted Rat Retained PU Mass (mg)	2.65	8.43	23.3
Predicted Rat Retained PU Mass / PU SA (mg/m^2)	13.2	42.2	117
Light Activity 40-Year HEC (mg/m^3)	0.74	2.35	6.5
Heavy Activity 40-Year HEC (mg/m^3)	0.36	1.14	3.16

HEC = human equivalent concentration that results in the same inhaled dose metric (retained PU mass / PU SA) as predicted for the rat. The human ventilatory parameters of the light and heavy activity levels for simulation of 40-year occupational scenario are described in the text.

Table [SEQ Table * ARABIC]. MPPD predictions and HEC calculations for a

hypothetical PVC exposure to F344 Rats with a particle MMAD of 10 μm, GSD of 2.07, and density of 1.3 gm / cm^3.

Exposure Concentration (mg/m^3)	3.3	8.3	20.2
Predicted Rat Retained PU Mass (mg)	0.024	0.073	0.23
Predicted Rat Retained PU Mass / PU SA (mg/m^2)	0.12	0.36	1.15
Light Activity 40-Year HEC (mg/m^3)	0.058	0.177	0.560
Heavy Activity 40-Year HEC (mg/m^3)	0.011	0.034	0.109

HEC = human equivalent concentration that results in the same inhaled dose metric (retained PU mass / PU SA) as predicted for the rat. The human ventilatory parameters of the light and heavy activity levels for simulation of 40-year occupational scenario are described in the text.

Message

From: Keene, Athena [Athena.Keene@AftonChemical.com]
Sent: 7/30/2020 3:37:53 PM
To: Kennedy, Wayne [Wayne.Kennedy@AftonChemical.com]; Rick_Becker@americanchemistry.com; Stedeford, Todd [Stedeford.Todd@epa.gov]; Sahar_Osman-Sypher@americanchemistry.com; Hayes, Michael [hayes.mp@pg.com]; Hillebold, Donna [donna.hillebold@nouryon.com]; ljovanovich@stepan.com; Moors, Stefan [stefan.moors@basf.com]; Ogden, Julianne [Julianne_Ogden@americanchemistry.com]; Skulsky, Joseph [JSkulsky@stepan.com]; Washburn, Kenneth [Kenneth.Washburn@us.sasol.com]; Yang, Xinyu [xyang@Solenis.com]; Tveit, Ann [Ann.Tveit@basf.com]; Irwin, William [Irwin.William@epa.gov]; Salazar, Keith [Salazar.Keith@epa.gov]; Henry, Tala [Henry.Tala@epa.gov]; Jarabek, Annie [Jarabek.Annie@epa.gov]
Subject: RE: Revised draft surfactants manuscript - please see attached
Attachments: ATT00001.txt; Supporting Information File - 28 July 2020.ver.1 - AMK.docx; draft manscript general surfactants - 29 July 2020.ver.3 - AMK.docx

Hi Todd,

Ex. 5 Deliberative Process (DP)

Kind regards,
Athena

From: Kennedy, Wayne
Sent: Thursday, July 30, 2020 10:49 AM
To: Becker, Rick <Rick_Becker@americanchemistry.com>; Stedeford, Todd <Stedeford.Todd@epa.gov>; Osman-Sypher, Sahar <Sahar_Osman-Sypher@americanchemistry.com>; Hayes, Michael <hayes.mp@pg.com>; Hillebold, Donna <donna.hillebold@nouryon.com>; Jovanovich, Lela <ljovanovich@stepan.com>; Keene, Athena <Athena.Keene@AftonChemical.com>; Moors, Stefan <stefan.moors@basf.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Skulsky, Joseph <JSkulsky@stepan.com>; Washburn, Kenneth <Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Tveit, Ann <Ann.Tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>
Subject: RE: Revised draft surfactants manuscript - please see attached

Hello Todd,

Ex. 5 Deliberative Process (DP)

Regards,

Wayne

Wayne Kennedy | **Afton Chemical Corporation** | **Senior Manager – Product Stewardship and Regulatory Affairs**

500 Spring Street, Richmond, VA 23219 | (804) 788-6035 | wayne.kennedy@aftonchemical.com

From: Becker, Rick <Rick_Becker@americanchemistry.com>
Sent: Thursday, July 30, 2020 10:23 AM
To: Stedeford, Todd <Stedeford.Todd@epa.gov>; Osman-Sypher, Sahar <Sahar_Osman-Sypher@americanchemistry.com>; Hayes, Michael <hayes.mp@pg.com>; Hillebold, Donna <donna.hillebold@nouryon.com>; Jovanovich, Lela <ljovanovich@stepan.com>; Keene, Athena <Athena.Keene@AftonChemical.com>; Kennedy, Wayne <Wayne.Kennedy@AftonChemical.com>; Moors, Stefan <stefan.moors@basf.com>; Ogden, Julianne <Julianne_Ogden@americanchemistry.com>; Skulsky, Joseph <JSkulsky@stepan.com>; Washburn, Kenneth <Kenneth.Washburn@us.sasol.com>; Yang, Xinyu <xyang@Solenis.com>; Tveit, Ann <Ann.Tveit@basf.com>; Irwin, William <Irwin.William@epa.gov>; Salazar, Keith <Salazar.Keith@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Jarabek, Annie <Jarabek.Annie@epa.gov>
Subject: Revised draft surfactants manuscript - please see attached

Hi Todd - please see attached. I didn't see anything that was a true show stopper.

Ex. 5 Deliberative Process (DP)

But since time is tight, if not able to include these with the submission, we can address these when doing the revision in response to peer reviewers comments.

Ex. 5 Deliberative Process (DP)

Thanks

Rick

Richard A. Becker Ph.D. DABT | American Chemistry Council
Science and Research Division
rick_becker@americanchemistry.com
700 2nd Street, NE | Washington, DC | 20002
O: (202) 249-6405
Cell: **Ex. 6 Personal Privacy (PP) - personal phone**
www.americanchemistry.com

From: Stedeford, Todd [mailto:Stedeford.Todd@epa.gov]
Sent: Wednesday, July 29, 2020 4:18 PM
To: Osman-Sypher, Sahar; Becker, Rick; Hayes, Michael; Hillebold, Donna; Jovanovich, Lela; Keene, Athena M.; Kennedy, Wayne; Moors, Stefan; Ogden, Julianne; Skulsky, Joseph; Washburn, Kenneth; Yang, Xinyu; Tveit, Ann; Irwin, William; Salazar, Keith; Henry, Tala; Jarabek, Annie
Subject: Revised draft surfactants manuscript
Importance: High

All,

Please find the attached, revised draft of the surfactants manuscript. This still needs a good critical review by multiple sets of eyes. This is a standalone document. It contains all of the tables. I linked up everything with the exception of the POD table. I still need to link the references in that table with EndNote. Otherwise, please review as quickly as you can.

Thank you,

Todd

Surfactants Category: The Application of New Approach Methodologies (NAMs) for Assessing Inhalation Risks under the Amended Toxic Substances Control Act

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[b] Risk Assessment Division, Office of Pollution Prevention and Toxics, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, DC 20460, United States

[c] Proctor & Gamble, Company, Inc., St. Bernard, Ohio 45217, Untied States; Temselaan 100, 1853 Strombeek-Beaver, Belgium

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KEYWORDS (Word Style "BG_Keywords"). If you are submitting your paper to a journal that requires keywords, provide significant keywords to aid the reader in literature retrieval.

ABSTRACT

The Toxic Substances Control Act (TSCA) requires anyone who plans to manufacture (including import) a new chemical substance for a non-exempt commercial purpose to provide EPA with a premanufacture notice (PMN) before initiating the activity. Surfactants are a class of chemicals commonly used in occupational settings, in consumer products and in biological research and development and therefore subject to PMN. Their uses in such applications provide pathways of exposure by which potential toxicity of these compounds may occur to humans. While TSCA requires submission of any existing toxicity data, it does not require generation of toxicity data for the purpose of or prior to PMN submission. TSCA requires EPA to review the PMN to determine whether the new chemical substance presents an unreasonable risk of injury to human health or

the environment and also mandates that EPA reduce and replace vertebrate animals in testing, to the extent practicable and scientifically justified. EPA therefore relies on a number of approaches that do not rely on *de novo* toxicity testing. Analogue read-across, in which toxicity data for a chemical of similar structure and activity is used to assess the new chemical, and chemical categories (a group of chemicals whose properties are likely to be similar or follow a regular pattern as a result of mechanism, mode of toxic action or structural similarity) have been used by EPA for decades to assess new chemical substances. This investigation was conducted to identify surfactant chemicals with toxicity data relevant for use in conducting a quantitative human health risk assessment for new surfactant substances and define a TSCA New Chemical Category for surfactants. Category boundaries are defined, toxicological analogues suitable for conducting 'read-across' hazard assessment (*i.e.*, –hazard identification and dose-response analysis) are identified and a tiered-testing strategy aimed at using new approach methodologies (NAMs) to reduce or replace animal testing is outlined. This surfactant category provides a pragmatic and scientifically defensible approach to facilitate EPA's review of new surfactant PMNs and a strategic testing approach that provides the data needed to conduct or refine surfactant risk assessment while also meeting the requirements of TSCA to reduce vertebrate testing.

INTRODUCTION

The Toxic Substances Control Act (TSCA) was amended in 2016 by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Pub. L. 114-182. The amended TSCA included substantial changes to EPA's authorities and responsibilities, including requirements on EPA to make a determination regarding sufficiency of information, production quantities relative to environmental releases and human exposure, and unreasonable risks. The amended TSCA also included provisions

mandating EPA "reduce and replace, to the extent practicable, scientifically justified" the use of vertebrate animals in the testing of chemicals substances. Specifically, TSCA section 4(h) charges EPA with encouraging and facilitating –

> (1) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions under TSCA;
> (2) the grouping of 2 or more chemical substances into scientifically appropriate categories in cases in which testing of a chemical substance would provide scientifically valid and useful information on other chemical substances in the category; and
> (3) the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests, provided that such consortia make all information from such testing available to the Administrator.

The present investigation advances each of these TSCA mandates for chemical substances characterized as surfactants.

A surfactant is a substance that reduces the surface tension of a liquid in which it is dissolved. They are surface-active, amphiphilic compounds that self-assemble to form micelles or aggregates above a critical concentration, referred to as the critical micelle concentration (CMC). These substances are commonly used in occupational settings, in consumer products (*e.g.*, household cleaning products, personal care products, *etc.*), and in biological research and development (R&D) as detergents, wetting agents, emulsifiers, foaming agents, and dispersants. Their use in such applications provide pathways of exposure by which potential toxicity of these

compounds may occur to human or environmental receptors. Specifically, the inherent properties of surfactants may induce toxicity if exposures occur such that they can interfere with biological surfactants or tissues. For example, sodium dodecyl sulfate, a strong anionic surfactant, is used in R&D applications at concentrations up to 10% to disrupt cell membranes and to denature proteins, whereas octylphenoxypolyethoxyethanol, a mild nonionic surfactant, is used in R&D applications at concentrations up to 1% to disrupt cell membranes, while preserving proteins for isolation [ADDIN EN.CITE <EndNote><Cite><Author>Burden</Author><Year>2012</Year><RecNum>14727</RecNum><DisplayText>[1]</DisplayText><record><rec-number>14727</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017177">14727</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Burden, D.W.</author></authors></contributors><titles><title>Guide to the Disruption of Biological Samples - 2012, Version 1.1.</title><secondary-title>Random Primers</secondary-title></titles><periodical><full-title>Random Primers</full-title></periodical><pages>1-25</pages><number>12</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

Hazard concerns for surfactants were historically focused on their observed environmental effects and potential toxicity to aquatic organisms [ADDIN EN.CITE ADDIN EN.CITE.DATA]. For example, the U.S. Environmental Protection Agency (EPA) established chemical categories for cationic (quaternary ammonium) and anionic surfactants based on environmental toxicity concerns [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>14729</RecNum><DisplayText>[3]</DisplayText><record><rec-number>14729</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017536">14729</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>TSCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>157, https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Surfactants may also be a potential hazard concern to humans, depending on the use and route of exposure, because they can disrupt the normal architecture of the lipid bilayer and reduce the surface tension, thereby solubilizing cell membranes. Mucous membranes are particularly sensitive to the surface-active effects of surfactants, which have been shown to cause irritancy and injury to the eye, based on their ability to “readily penetrate the sandwiched aqueous and lipid barriers of the cornea” [ADDIN EN.CITE <EndNote><Cite><Author>Fox</Author><Year>2008</Year><RecNum>14730</RecNum><DisplayText>[4]</DisplayText><record><rec-number>14730</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017801">14730</key></foreign-keys><ref-type name="Book

Section">5</ref-type><contributors><authors><author>Fox, D.A.</author><author>Boyes, W.K.</author></authors><secondary-authors><author>Klaassen, C.D.</author></secondary-authors></contributors><titles><title>Toxic Responses of the Ocular and Visual System</title><secondary-title>Casarett & Doull's Toxicology - The Basic Science of Poisons, Seventh Edition</secondary-title></titles><pages>665-697</pages><section>17</section><dates><year>2008</year></dates><pub-location>New York</pub-location><publisher>McGraw-Hill, Medical Publishing Division</publisher><urls></urls></record></Cite></EndNote>].

Depending on the conditions of use, inhalation exposures to workers and/or consumers may be possible that warrant consideration in quantitative risk assessments. As noted, surfactants may cause adverse effects on mucous membranes, including the respiratory tract, and have been shown to interfere with the natural pulmonary surfactants, resulting in reduced oxygen content of arterial blood (*i.e.*, impaired gas exchange in the lung), increases in pulmonary extravascular water volume and wet-to-dry weight ratio of the lungs, grossly visible pulmonary edema, and atelectasis [ADDIN EN.CITE ADDIN EN.CITE.DATA]. However, the chemical space for surfactants that may present inhalation hazards has not been previously defined, and the potential for inhalation toxicity ranges by orders of magnitude, such as octylphenoxypolyethoxyethanol, a nonionic surfactant 14-day lowest-observed-adverse-effect concentration [LOAEC] of 5.3 mg/m^3) [ADDIN EN.CITE ADDIN EN.CITE.DATA], versus didecyldimethyl ammonium chloride, a cationic surfactant and biocide (DDAC, CASRN 7173-51-5; 4-week lowest-observed-adverse-effect concentration [LOAEC] of 0.08 mg/m^3 for portal-of-entry effects) [ADDIN EN.CITE

<EndNote><Cite><Author>EPA</Author><Year>2016</Year><RecNum>14732</RecNum><DisplayText>[10]</DisplayText><record><rec-number>14732</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018482">14732</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Subchronic Inhalation Toxicity Study of DDAC - Revised</title><secondary-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>25</pages><volume>HQ-OPP-2006-0338-0045</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]

.

The objectives of the present investigation were to: (1) perform a systematic review of the literature with the aim of defining the chemical space for surfactants; (2) identify appropriate toxicological analogues, when available, for identifying potential inhalation hazards and when data allow, identifying quantitative point(s) of departure for use in an inhalation risk assessment; (3) describe scientifically sound new approach methodologies (NAMs) to reduce or replace animal testing, where possible; and (4) establish a tiered-testing strategy, that utilizes NAMs, as appropriate, for new chemistries in the surfactant space.

MATERIALS AND METHODS

Systematic Literature Review

Two literature searches were performed, an initial search in November 2016 and a supplemental search in April 2018. The details of these searches, including the search strategies, search terms, search results and Population, Exposure, Comparison, and Outcome (PECO) criteria used for reviewing the relevance of the results are provided in the Supporting Information file at "Section 1 Systematic Literature Review". These searchers were conducted with the primary objective of identifying studies that evaluated the toxicity of surfactants in respiratory tract in exposed humans, laboratory animals, and at the cellular level in *in vitro* and *ex vivo* studies. A secondary objective of these searches was to identify potential NAMs that could inform a tiered-testing strategy for general surfactants that reduces or replaces the use of vertebrate animals in regulatory testing.

Risk Assessment Approaches under TSCA

Risk Assessment Paradigm

The current methods and approaches for assessing risks of new chemical substances under TSCA have been built upon decades of expert development, scientific peer review, refinement, and scientific knowledge. Generally, EPA conducts risk assessments following the four-step process articulated by the National Research Council, first in 1983 [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>1983</Year><RecNum>14733</RecNum><DisplayText>[11]</DisplayText><record><rec-number>14733</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018654">14733</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>

Risk Assessment in the Federal Government: Managing the Process, Washington, D.C. The National Academies Press</title></titles><pages>191, DOI: https://doi.org/10.17226/366</pages><volume>ISBN: 978-0-309-03349-7</volume><dates><year>1983</year></dates><urls></urls></record></Cite></EndNote>] and reaffirmed several times since [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>1994</Year><RecNum>14734</RecNum><DisplayText>[12, 13]</DisplayText><record><rec-number>14734</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596018772">14734</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Science and Judgment in Risk Assessment, Washington, D.C. The National Academies Press</title></titles><pages>672, DOI: https://doi.org/10.17226/2125</pages><volume>ISBN: 978-0-309-07490-2</volume><dates><year>1994</year></dates><urls></urls></record></Cite><Cite><Author>NRC</Author><Year>2009</Year><RecNum>14737</RecNum><record><rec-number>14737</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019010">14737</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Science and Decisions: Advancing Risk Assessment, Washington, D.C. The National Academies Press</title></titles><pages>422, DOI: https://doi.org/10.17226/12209</pages><volume>ISBN: 978-0-309-12046-

3</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. This process includes hazard identification, dose-response analysis, exposure assessment, and risk characterization. Hazard assessment (also called effects assessment in some EPA guidance documents) identifies the types of adverse health or environmental effects or hazards that can be caused by exposure to the chemical substance. The dose-response assessment describes the relationship between the exposure or dose of a chemical and the occurrence of health or environmental effects or outcomes is assessed. The exposure assessment characterizes the extent of human or environmental exposures, including the magnitude, frequency, and duration of the exposure, to the extent necessary and practicable within the context of the assessment. Finally, the risk characterization integrates the hazard, dose-response, and exposure components to describe the nature, and when possible, the magnitude of risks to human health and the environment.

The approaches employed for these components, including, for example, the level of detail and complexity of quantitative aspects may vary across different risk assessments and typically align with specific legislative and regulatory frameworks. For example, legislative and regulatory frameworks for hazard evaluation of pesticide active ingredients, anti-microbial substances, inerts, *etc*. are described in regulations for pesticides, which include multiple and specific requirements for toxicity data. Under TSCA and its implementing regulations [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2020</Year><RecNum>14738</RecNum><DisplayText>[14]</DisplayText><record><rec-number>14738</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr"

timestamp="1596019129">14738</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA </author></authors></contributors><titles><title>40 CFR Part 720 - Premanufacture Notification</title><secondary-title>Code of Federal Regulations</secondary-title></titles><periodical><full-title>Code of Federal Regulations</full-title></periodical><pages>https://www.law.cornell.edu/cfr/text/40/part-720</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], companies are required to submit a Premanufacture Notice (PMN) along with all available data on: chemical identity, production volume, byproducts, use, environmental release, disposal practices, and human exposure. These submissions are required to include all existing health and environmental data in the possession or control of the submitter, parent company, or affiliates, and a description of any existing data known to or reasonably ascertainable by the submitter. However, TSCA has never included requirements for toxicity testing or generation of hazard data for new chemical substances prior to submission for review by EPA.

Hazard Assessment

Given the lack of toxicity testing requirements under TSCA, EPA only occasionally receives human health relevant hazard data for new chemical substances. EPA conducted an analysis of toxicity tests submitted to EPA from 2004 through 2012 for new chemical substances under TSCA and found that about 15% of the PMN submissions included some type of human health relevant hazard data,[5] mostly animal tests for acute toxicity and irritation. TSCA provides EPA with the authority to require generation and submission of additional data when the information included with the PMN, coupled with that available to EPA risk assessors from prediction

modeling, read-across, internal archives, *etc*. is insufficient to permit a reasoned evaluation of the health and environmental effects of a new chemical substance. However, prior to making a request for testing using vertebrate animals, EPA must take into consideration reasonably available existing information, including toxicity information; computational toxicology and bioinformatics; and high-throughput screening methods and the prediction models of those methods (TSCA Section 4(h)(A)(i)-(iii)).

Given the historical lack of hazard data and the new requirements to consider reasonably available existing information, EPA has, for decades, relied on a number of approaches that do not rely on *de novo* toxicity testing, including computational toxicology (*e.g.*, predictive models and expert systems), analogue read-across (wherein available toxicity data for a chemical of similar structure and activity is used to assess the new chemical substance lacking data), and chemical categories (a group of chemicals whose properties are likely to be similar or follow a regular pattern as a result of mechanism, mode of toxic action or structural similarity) [ADDIN EN.CITE <EndNote><Cite><Author>van Leeuwen</Author><Year>2009</Year><RecNum>14739</RecNum><DisplayText>[15]</DisplayText><record><rec-number>14739</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019290">14739</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>van Leeuwen, K.</author><author>Schultz, T. W.</author><author>Henry, T.</author><author>Diderich, B.</author><author>Veith, G. D.</author></authors></contributors><auth-address>TNO Quality of Life, Utrechtseweg 48, The Netherlands.</auth-address><titles><title>Using chemical categories to fill data gaps in

hazard assessment</title><secondary-title>SAR QSAR Environ Res</secondary-title><alt-title>SAR and QSAR in environmental research</alt-title></titles><periodical><full-title>SAR QSAR Environ Res</full-title><abbr-1>SAR and QSAR in environmental research</abbr-1></periodical><alt-periodical><full-title>SAR QSAR Environ Res</full-title><abbr-1>SAR and QSAR in environmental research</abbr-1></alt-periodical><pages>207-20</pages><volume>20</volume><number>3-4</number><edition>2009/06/23</edition><keywords><keyword>Hazardous Substances/pharmacology/*toxicity</keyword><keyword>*Quantitative Structure-Activity Relationship</keyword><keyword>Safety Management/*methods</keyword></keywords><dates><year>2009</year></dates><isbn>1026-776x</isbn><accession-num>19544189</accession-num><urls></urls><electronic-resource-num>10.1080/10629360902949179</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. The integration of these methods with NAMs to advance testing strategies has been recognized by EPA [ADDIN EN.CITE ADDIN EN.CITE.DATA] and is consistent with the vision articulated in the 2007 report by the National Research Council in "Toxicity Testing in the 21st Century: A Vision and Strategy [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2007</Year><RecNum>14741</RecNum><DisplayText>[17]</DisplayText><record><rec-number>14741</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019531">14741</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>NRC</author></authors></contributors><titles><title>T oxicity Testing in the 21st Century: A Vision and a Strategy, Washington, D.C. The National Academies Press</title></titles><pages>216, DOI: https://doi.org/10.17226/11970</pages><volume>ISBNs: Ebook: 978-0-309-13412-5; Paperback: 978-0-309-15173-3</volume><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>].

Dose-Response Analysis

For assessing hazards to human health, EPA relies most heavily on read-across methods using an analogue or a category of analogues to identify hazards and conduct dose-response analysis to identify a point of departure (POD). While EPA has a number of existing "TSCA New Chemicals Program (NCP) Chemical Categories" [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2010</Year><RecNum>14729</RecNum><DisplayText>[3]</DisplayText><record><rec-number>14729</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596017536">14729</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>T SCA New Chemicals Program (NCP) Chemical Categories</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>157, https://www.epa.gov/sites/production/files/2014-

10/documents/ncp_chemical_categories_august_2010_version_0.pdf</pages><dates><year>201
0</year></dates><urls></urls></record></Cite></EndNote>], including for anionic, nonionic,
and cationic surfactants, the existing surfactant categories were developed and defined based
only on environmental toxicity considerations. Toxicity tests for analogues are used to identify a
point of departure (POD) (*i.e.,* a dose or concentration that marks the beginning of a low-dose
extrapolation) for assessing risks to the new chemical substance. This point can be the lower
bound on dose for an estimated incidence or a change in response level from a dose-response
model (*i.e.*, benchmark concentration or dose [BM(C)D], NOAE(C)L, LOAE(C)L, or human
equivalent concentration or dose [HE(C)D]) for an observed incidence or change in level of
response) [ADDIN EN.CITE
<EndNote><Cite><Author>EPA</Author><Year>2012</Year><RecNum>14744</RecNum><
DisplayText>[18]</DisplayText><record><rec-number>14744</rec-number><foreign-
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Agency, Washington, D.C. 20460</full-title></periodical><pages>99,
https://www.epa.gov/sites/production/files/2015-
01/documents/benchmark_dose_guidance.pdf</pages><volume>EPA/100/R-

12/001</volume><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>].

Once suitable analogues are identified, the strengths, limitations, and uncertainties associated with using the analogue as predictive of hazards of the new chemical substance are considered to derive a benchmark margin of exposure (MOE). The benchmark MOE is the result of multiplying all relevant uncertainty factors (UFs) to account for: (1) the variation in susceptibility among the members of the human population (*i.e.*, inter- individual or intraspecies variability); (2) the extrapolation from animal data to humans (*i.e.*, interspecies extrapolation); (3) the extrapolation from data in a study with less- than- lifetime exposure (*i.e.*, extrapolating from sub-chronic to chronic exposure); (4) the extrapolation from a LOAEL rather than from a NOAEL [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2002</Year><RecNum>14743</RecNum><DisplayText>[19, 20]</DisplayText><record><rec-number>14743</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019884">14743</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>A Review of the Reference Dose and Reference Concentration Processes</title><secondary-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>192, https://www.epa.gov/sites/production/files/2014-

12/documents/rfd-final.pdf</pages><volume>EPA/630/P-02/002F</volume><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>EPA</Author><Year>2014</Year><RecNum>14742</RecNum><record><rec-number>14742</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019768">14742</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation</title><secondary-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>109, https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf</pages><volume>EPA/R-14/002F</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. EPA prefers using existing information to develop data-derived extrapolation factors or chemical specific adjustment factors (DDEFs or CSAFs) rather than simply relying on defaults [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2014</Year><RecNum>14742</RecNum><DisplayText>[20]</DisplayText><record><rec-number>14742</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596019768">14742</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation</title><secondary-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of the Science Advisor, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>109, https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf</pages><volume>EPA/R-14/002F</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. This investigation includes a number of approaches to derive DDEFs to use in assessing new surfactant chemical substances.

Exposure Assessment

In assessing new chemical substances, EPA typically generates the human exposure estimates for workers using modeling approaches including the Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER). ChemSTEER exposure estimates are generated as daily acute potential dose rates (PDRs) or lifetime average daily doses (LADDs). Given that new chemical substances will not have occupational exposure monitoring data, except for possible monitoring data on analogues, the PDR is typically used as an initial conservative exposure estimate when calculating the MOE.

Commented [HT1]: Mppd guidance

Due to the surface-activity of surfactants at the point of exposure, the PDR is the appropriate dose-metric rather than the LADD which is typically used to assess cancer risks. For chemical substances used in a liquid, mist, or aerosol form, the general default PDR value is 1.875 mg/kg-

Commented [HT2]: But why? Due to long term/chronic exposure?

Commented [HT3]: Does this need more explaination? the PDR is mg/kg per day; so using repeated dose tox studies adjusted to # of days exposure. NOT using acute animal data

Tala and Marc Odin comment: explain why PDDR is appropriate

bw/day for inhalable aerosols or 0.625 mg/kg-bw/day for respirable aerosols calculated using the default values as shown in [REF _Ref46930162 \h * MERGEFORMAT] [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2015</Year><RecNum>14745</RecNum><DisplayText>[21]</DisplayText><record><rec-number>14745</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021217">14745</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>ChemSTEER User Guide, Chemical Screening Tool for Exposures and Environmental Releases</title><secondary-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>403, https://www.epa.gov/sites/production/files/2015-05/documents/user_guide.pdf</pages><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

Table [SEQ Table * ARABIC]. Default values used for calculating the PDR.

Description	Equation	Description	Equation[a]	Defaults	Units
PDR (mg/kg-bw/day)	I/BW	Inhalation PDR (I)	Cm × b × h, where Cm is the mass concentration of chemical in air, b is the volumetric inhalation rate ($0 < b \leq 7.9$), and h is the exposure duration ($0 \leq h \leq 24$)	Cm = 15 mg/m^3 b = 1.25 m^3/hr h = 8 hours/day	mg/day
		Body weight (BW)	BW ($0 \leq BW$)	80 kg-bw	kg-bw

[a] Cm may also be adjusted for the mass concentration of the chemical with a PEL in air (based on OSHA PEL – TWA; default = 15 mg/m^3 inhalable; 5 mg/m^3 for respirable, the weight fraction of chemical in particulate (Ys) ($0 < Ys \leq 1$), the weight fraction of chemical or metal with a PEL in particulate (Ypel) ($0 < Ypel \leq 1$) using the following equation: Cm = KCk × Ys/Ypel

The PDR is calculated using a default worker values of 8 hrs/day and 5 days/week, unless chemical-specific manufacture, processing or use information are provided in the PMN. The exposure regimen used in animal studies often do not reflect occupational exposure scenarios, such that a duration adjustment and a dosimetric factor (*i.e.,* RDDR value) is applied to the POD from the animal study to derive human equivalent concentrations (HECs) exposed human population. While this adjustment would optimally be made using physiologically-based pharmacokinetic model [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>1994</Year><RecNum>14746</RecNum><DisplayText>[22]</DisplayText><record><rec-number>14746</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021628">14746</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</title><secondary-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</secondary-title></titles><periodical><full-title>Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC</full-title></periodical><pages>389, https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf</pages><volume>EPA/600/8-90/066F</volume><dates><year>1994</year></dates><urls></urls></record></Cite></EndNote>], the data required to conduct such modelling rarely exist for new chemical substances.

Therefore, occupational exposures are adjusted using particle deposition models with human exertion (work) ventilation rates and exposure durations appropriate to the particular occupational setting and chemical use scenario.

Risk Characterization

Risk characterization is an integral component of the risk assessment process for both ecological and health risks, *i.e.*, it is the final, integrative step of risk assessment. As defined in EPA's Risk Characterization Policy, the risk characterization integrates information from the hazard and exposure components of the risk assessment and synthesizes an overall conclusion about risk that is complete, informative, and useful for decision-making. A risk characterization conveys the risk assessor's judgment as to the nature and existence of (or lack of) human health or ecological risks [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2000</Year><RecNum>14747</RecNum><DisplayText>[23]</DisplayText><record><rec-number>14747</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596021806">14747</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>EPA</author></authors></contributors><titles><title>Risk Characterization</title><secondary-title>Office of Science Policy, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. 20460</secondary-title></titles><periodical><full-title>Office of Science Policy, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. 20460</full-title></periodical><pages>189,

https://nepis.epa.gov/Exe/ZyPDF.cgi/40000006.PDF?Dockey=40000006.PDF</pages><volume>EPA 100-B-00-002</volume><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>]. As noted in EPA's Risk Characterization Handbook "Risk characterization at EPA assumes different levels of complexity depending on the nature of the risk assessment being characterized. The level of information contained in each risk characterization varies according to the type of assessment for which the characterization is written and the audience for which the characterization is intended."

Under TSCA section 5, EPA must determine whether a chemical substance presents an unreasonable risk of injury to health or the environment under the conditions of use. EPA generally uses an MOE approach to characterize risks of new chemical substances as a starting point to estimate non-cancer risks for acute and chronic exposures. The MOE is the HEC derived from a POD for a specific health endpoint (from hazard assessment) divided by the exposure concentration for the specific scenario of concern (from exposure assessment). To determine whether the resulting MOE results in an adequate margin between human exposure estimates and the HEC derived from a POD, the MOE value is compared with a benchmark MOE. When using MOEs as risk estimates for non-cancer health effects, the benchmark MOEs are used to interpret the risk estimates. Generally, when the MOE is less than the benchmark MOE human health risks are interpreted as possible. On the other hand, negligible concerns would be expected if the MOE exceeds the benchmark MOE. The MOE approach is a widely recognized point estimate method and allows for providing a risk profile for a range of different non-cancer health effects and different exposure scenarios.

In summary, to conduct a risk evaluation for new chemical substances, as required under TSCA section 5, EPA conducts a hazard assessment, using empirical data when available, but most often using analogues, to identify a POD(s) and to develop a benchmark MOE that reflects specific uncertainties associated with data available for use in the evaluation. This hazard assessment is combined with the exposure assessment, to calculate an MOE, which is compared to the benchmark MOE to determine whether risks are identified. The risk characterization is used to inform the "unreasonable risk" determination.

Commented [KA4]: This is a bit confusing. Is the benchmark MOE a standard value or is it also calculated as part of the risk assessment?

RESULTS AND DISCUSSION

Literature Search and Screening Results

The initial PubMed search identified 594 articles that were subjected to title and abstract screening. Of these, 551 did not meet the PECO criteria, whereas 43 met the PECO criteria and were selected for full text review. An additional 17 references were included for full text review that met the PECO criteria and were identified through additional search strategies, screening gray literature, references for other types of chemical substances, *etc*. Of the 60 articles evaluated through full text screening, ~~16~~ 25 were identified as relevant and carried forward in the present evaluation, whereas the remaining ~~44~~ 35 studies were excluded because they lacked relevant information on respiratory tract effects or presented inconclusive epidemiology findings. In the supplemental literature search, 1242 studies were identified on PubMed and Embase (combined). Following title and abstract screening, 1217 of these studies were excluded because they did not meet the PECO criteria. A total of 35 studies (including 10 studies found by additional hand searching) met the

Commented [KA5]: The updates here are further described in the SI.

Commented [KA6]: The numbers in this section need to be checked. The PubMed and Embase search appears to include 1247 references.

Commented [KA7]: 1242-1217 is 25 studies that met the PECO criteria but then 10 additional studies were found.

PECO criteria and were selected for full text screening, which resulted in 25 studies that were identified for review and 10 studies that were deemed irrelevant and excluded. Of the 25 studies identified for review, ~~15 of the studies were identified in the initial literature search~~9 of the studies were additional studies from the supplemental literature search.

Commented [KA8]: I edited this since there was one study that was in the EPA search but removed from the TS search since it was only available in Japanese.

The information identified in the systematic review was used to inform the section on Category Boundaries and subcategories with the boundaries, to summarize the health effects of surfactants under the section on Hazard Identification, and to identify potential NAMs for use in the section on Tiered-Testing Strategies.

Category Boundaries

The following structural and functional criteria (hereinafter referred to as the "Surfactant Criteria") are used to distinguish chemical substances, which include polymers and UVCB substances,[1] intended for use as surfactants from other amphiphilic compounds (*e.g.*, ethanol) [ADDIN EN.CITE ADDIN EN.CITE.DATA]:

1. A substance which has surface-active properties, and which consists of one or more hydrophilic and one or more hydrophobic groups;
2. The substance must be capable of reducing the surface tension between air and water to 45 milliNewtons/meter (mN/m) or below at a test condition of 0.5 wt% in water and a temperature of 20°C (*Cf.* Pure water has a surface tension of 72.8 mN/m at 20°C); and

[1] Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB Substance)

3. The substance self-associates in water to form micellar or vesicular aggregates at a concentration of 0.5 wt% or below.

The Surfactants Category is further defined into three general subcategories including nonionic, anionic, and cationic substances. Within these subcategories, The Surfactant Category is subcategorized for those chemical substances that initially meet the Surfactant Criteria and possess ionic or nonionic properties, as discussed below. Note, though not listed in the following subcategories, amphoteric chemical substances that meet the Surfactant Criteria would also be included within these subcategories (*i.e.*, cationic or anionic surfactants), depending on their pH. Lung lining fluids are near neutral pH, with various measurements ranging from 6.6 to 7.1 [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The pKa for each component of an amphoteric surfactant should be considered within this pH range and the assessment should be conducted on the predominant components. The non-ionized fraction for acids/bases should be calculated as follows:

$$\text{Acids Fraction}_{\text{non-ionized}} = 1 / (1 + 10^{\text{pH-pKa}})$$

$$\text{Bases Fraction}_{\text{non-ionized}} = 1 / (1 + 10^{\text{pKa-pH}})$$

Where the pH represents the physiological pH in the lung (*i.e.*, 6.6 to 7.1), and the pKa represents the value for the respective component (*e.g.*, carboxylic acid or amine).

Nonionic surfactants are identified as any neutral chemical substance that meets the Surfactant Criteria. Common nonionic surfactants include alkylphenol chemical substances with one or more than one ethoxylate (EO) unit as well as linear and branched alcohol chemical substances with one or more EO units. For example, octylphenoxypolyethoxyethanol, a common nonionic octylphenol EO surfactant, and Polysorbate 80 (or Tween 80), another nonionic alkyphenol ethoxylate with increased alkyl chain length and number of EO units, are shown in [REF _Ref46930277 \h * MERGEFORMAT]. The surface tensions of octylphenoxypolyethoxyethanol and Polysorbate 80 range from 30-31 mN/m to 37.96 mN/m, respectively ([REF _Ref46930277 \h * MERGEFORMAT]) [ADDIN EN.CITE <EndNote><Cite><Author>Kothekar</Author><Year>2007</Year><RecNum>14758</RecNum><DisplayText>[30]</DisplayText><record><rec-number>14758</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025228">14758</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kothekar, S.C.</author><author>Ware, A.M.</author><author>Waghmare, J.T.</author><author>Momin, S.A.</author></authors></contributors><titles><title>Comparative Analysis of the Properties of Tween-20, Tween-60, Tween-80, Arlacel-60, and Arlacel-80</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><periodical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>477-484, https://www.tandfonline.com/doi/abs/10.1080/01932690601108045</pages><volume>28</volume><number>3</number><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>].

Anionic surfactants were identified as any chemical substance with a net negative charge that meets the Surfactant Criteria (*e.g.*, alkyl sulfonates, alkylbenzene sulfonates, alkylether sulfates, alkyl silicic acids, alkyl phosphates, alkyl carboxylic acids, or combinations of these anionic groups). The surface tension of SDS is reported to be 35 mN/m ([REF _Ref46930277 \h * MERGEFORMAT]).

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[HYPERLINK "http://hera.ugr.es/doi/15008447.pdf"]
this paper shows ST to be a lot higher

Cationic surfactants are identified as any chemical substance with a net positive charge that meets the Surfactant Criteria (*e.g.*, alkylammonium chlorides and benzalkonium chlorides). DDAC is a a representative member of this subcategory, although as noted previously, it also possesses biocidal properties. The surface tension of DDAC is reported to be 27.61 mN/m ([REF _Ref46930277 \h * MERGEFORMAT]).

Table [SEQ Table * ARABIC]. Example Chemicals that Meet "Surfactant Criteria" and Nonionic, Anionic and Cationic Subcategorization.

Nonionic Surfactants					
Chemical Name in Text	**Other Relevant Names**	**Criteria 1**		**Criteria 2**	**Criteria 3**
		Hydrophobic group(s)	**Hydrophilic group(s)**	**Surface Tension**	**Critical Micel Concentration (CMC)**
Octoxynol 9 CASRN 9002-93-1	Triton X-100 Octylphenol ethoxylate CAS Name: Poly(oxy-1,2-ethanediyl), .alpha.-[4-1,1,3,3-tetramethylbutyl)phenyl]-.omega.-hydroxy	octylphenol group	polyoxyethylene (9) unit	~30.5 mN/m at 5 g/L (0.5 wt%) and 25°C* [ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sch	0.17 g/L or 0.01 wt% [ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal

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				ott, H.</author></authors></contributors><auth-address>School of Pharmacy, Temple University, Philadelphia, Pennsylvania, 19140</auth-address><titles><title>Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)</title><secondary-title>J Colloid Interface Sci</secondary-title><alt-title>Journal of colloid and interface science</alt-title></titles><periodical><full-title>Journal of colloid and interface	Article">17</ref-type><contributors><authors><author>Schott, H.</author></authors></contributors><auth-address>School of Pharmacy, Temple University, Philadelphia, Pennsylvania, 19140</auth-address><titles><title>Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)</title><secondary-title>J Colloid Interface Sci</secondary-title><alt-title>Journal of

				science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></periodical><alt-periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></alt-periodical><pages>496-502</pages><volume>205</volume><number>2</number><edition>1998/12/16</edition><dates><year>1998</year><pub-dates><date>Sep 15</date></pub-dates></dates><isbn>0021-9797</isbn><accession-num>9735215</accession-num><urls></urls><electronic-resource-num>10.1006/jcis.1998.5721</electronic-resource-	colloid and interface science</alt-title></titles><periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></periodical><alt-periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></alt-periodical><pages>496-502</pages><volume>205</volume><number>2</number><edition>1998/12/16</edition><dates><year>1998</year><pub-dates><date>Sep 15</date></pub-dates></dates><isb

				num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]	n>0021-9797</isbn><accession-num>9735215</accession-num><urls></urls><electronic-resource-num>10.1006/jcis.1998.5721</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]
Tyloxapol Defomaire Alevaire CASRN 25301-02-4	CAS Name: Formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol	multiple octyl phenol groups	multiple polyoxyethylene (9) units	~37 mN/m at 5 g/L (0.5 wt%) and 25°C* [ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-keys><key app="EN" db-	0.038 g/L or 0.0038 wt% [ADDIN EN.CITE <EndNote><Cite><Author>Schott</Author><Year>1998</Year><RecNum>14754</RecNum><DisplayText>[31]</DisplayText><record><rec-number>14754</rec-number><foreign-

				id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schott, H.</author></authors></contributors><auth-address>School of Pharmacy, Temple University, Philadelphia, Pennsylvania, 19140</auth-address><titles><title>Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)</title><secondary-title>J Colloid	keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024000">14754</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schott, H.</author></authors></contributors><auth-address>School of Pharmacy, Temple University, Philadelphia, Pennsylvania, 19140</auth-address><titles><title>Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton

				Interface Sci</secondary-title><alt-title>Journal of colloid and interface science</alt-title></titles><periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></periodical><alt-periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></alt-periodical><pages>496-502</pages><volume>205</volume><number>2</number><edition>1998/12/16</edition><dates><year>1998</year><pub-dates><date>Sep 15</date></pub-dates></dates><isbn	X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)</title><secondary-title>J Colloid Interface Sci</secondary-title><alt-title>Journal of colloid and interface science</alt-title></titles><periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></periodical><alt-periodical><full-title>Journal of colloid and interface science</full-title><abbr-1>J Colloid Interface Sci</abbr-1></alt-periodical><pages>496-

				>0021-9797</isbn><accession-num>9735215</accession-num><urls></urls><electronic-resource-num>10.1006/jcis.1998.5721</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]	502</pages><volume>205</volume><number>2</number><edition>1998/12/16</edition><dates><year>1998</year><pub-dates><date>Sep 15</date></pub-dates></dates><isbn>0021-9797</isbn><accession-num>9735215</accession-num><urls></urls><electronic-resource-num>10.1006/jcis.1998.5721</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]
Polyoxyethylene-10-oleyl ether	$C_{18:1}E_{10}$ Oleyl ethoxylate	oleyl group	polyoxyethylene (10) unit	35.17 mN/m at 4×10^{5} M (0.028%) and 25°C* [ADDIN EN.CITE	4×10^{-5} M or 0.028 wt % at 25°C [ADDIN EN.CITE <EndNote><Cite><

CASRN 9004-98-2	CAS Name: Poly(oxy-1,2-ethanediyl), .alpha.-(9Z)-9-octadecen-1-yl-.omega.-hydroxy			<EndNote><Cite><Author>Liu</Author><Year>2006</Year><RecNum>14761</RecNum><DisplayText>[32]</DisplayText><record><rec-number>14761</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025582">14761</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Liu, F.</author><author>Wang, Z.</author><author>Sun, D.</author><author>Wei, X.</author><author>Zhou, W.</author><author>Li, G.</author><author>Zhang,	Author>Liu</Author><Year>2006</Year><RecNum>14761</RecNum><DisplayText>[32]</DisplayText><record><rec-number>14761</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025582">14761</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Liu, F.</author><author>Wang, Z.</author><author>Sun, D.</author><author>Wei, X.</author><author>Zhou, W.</author><autho

				G.</author></authors></contributors><titles><title>Adsorption Kinetics of Brij 97 at the Air/Solution Interface</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><periodical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>657-663, https://www.tandfonline.com/doi/abs/10.1080/01932690600660624</pages><volume>27</volume><number>5</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>]	r>Li, G.</author><author>Zhang, G.</author></authors></contributors><titles><title>Adsorption Kinetics of Brij 97 at the Air/Solution Interface</title><secondary-title>Journal of Dispersion Science and Technology</secondary-title></titles><periodical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>657-663, https://www.tandfonline.com/doi/abs/10.1080/01932690600660624</pages><volume>27</volume><number>5</number><dates><year>2006</year></dates><urls></urls></

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					record></Cite></EndNote>]
Polyoxyethylene-10-dodecyl ether CASRN: 9002-92-0	$C_{12}E_{10}$ Polyoxyethylene (10) lauryl ether CAS Name: Poly(oxy-1,2-ethanediyl),-.alpha.-dodecyl-.omega.-	dodecyl group	polyoxyethylene (10) unit	C12E9: 36 mN/m at 23°C* C12E12: 32 mN/m at 23°C* [ADDIN EN.CITE <EndNote><Cite><Author>Rosen</Author><Year>1989</Year><RecNum>14763</RecNum><DisplayText>[33]</DisplayText><record><rec-number>14763</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026543">14763</key></foreign-keys><ref-type name="Edited Book">28</ref-type><contributors><authors><author>Rosen, M.J.</author></authors></contributors><titles><title>Surfactant	12.7×10^{-6} M or 0.0008 wt% at 30°C [ADDIN EN.CITE <EndNote><Cite><Author>Sulthana Author><Year>2000</Year><RecNum>14762</RecNum><DisplayText>[34]</DisplayText><record><rec-number>14762</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596025808">14762</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sulthana, S.B.</author><author>Rao,

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					ges><volume>16</volume><number>3</number><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>] Also, C12E9 at 1×10^{-6} M at 23°C and C12E12 at 1.4×10^{-6} M at 23°C [ADDIN EN.CITE <EndNote><Cite><Author>Rosen</Author><Year>1989</Year><RecNum>14763</RecNum><DisplayText>[33]</DisplayText><record><rec-number>14763</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026543">14763</key></foreign-keys><ref-type name="Edited

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Polysorbate 20 or Tween 20 CASRN 9005-64-5	Polyoxyethylene (20) sorbitan monolaurate CAS Name: Sorbitan, monododecanoate, poly(oxy-1,2-ethanediyl) derivs.	dodecanoyl group	sorbitan polyoxyethylene (20) unit	38 mN/m at 8.04×10^{-5} M (0.001%) and 21°C* [ADDIN EN.CITE <EndNote><Cite><Author>Kim</Author><Year>2001</Year><RecNum>14756</RecNum><DisplayTex	8.04×10^{-5} M or 0.001 wt% at 21°C [ADDIN EN.CITE <EndNote><Cite><Author>Kim</Author><Year>2001</Year><RecNum>14756</RecNum><DisplayText>[35]</Dis

				t>[35]</DisplayText><record><rec-number>14756</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024348">14756</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kim, C.</author><author>Hsieh, Y.-L.</author></authors></contributors><titles><title>Wetting and absorbency of nonionic surfactant solutions on cotton fabrics</title><secondary-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</secondary-title></titles><periodical><full-	playText><record><rec-number>14756</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024348">14756</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kim, C.</author><author>Hsieh, Y.-L.</author></authors></contributors><titles><title>Wetting and absorbency of nonionic surfactant solutions on cotton fabrics</title><secondary-title>Colloids and Surfaces A: Physicochemical and Engineering

				title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>385-397</pages><volume>187-188</volume><number>31</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>]	Aspects</secondary-title></titles><periodical><full-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>385-397</pages><volume>187-188</volume><number>31</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>]
Polysorbate 80 or Tween 80 CASRN 9005-65-6	Polyoxyethylene (20) sorbitan monooleate CAS Name: Sorbitan, mono-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) derivs.	octadecenoyl group	sorbitan polyoxyethylene (20) unit	37.96 mN/m at 5 g/L (0.5 wt %) and 30°C [ADDIN EN.CITE <EndNote><Cite><Author>Kothekar</Author><Year>2007</Year><RecNum>14758</RecNum><DisplayText>[30]</DisplayText><record><rec-number>14758</rec-number><foreign-keys><key app="EN"	1.5×10^{-5} M or 0.[Commented [HT16]: g/L?? wt% at 25°C [ADDIN EN.CITE <EndNote><Cite><Author>Mahmood</Author><Year>2013</Year><RecNum>14757</RecNum><DisplayText>[36]</DisplayText><record><rec-number>14757</rec-

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				ical><full-title>Journal of Dispersion Science and Technology</full-title></periodical><pages>477-484, https://www.tandfonline.com/doi/abs/10.1080/01932690601108045</pages><volume>28</volume><number>3</number><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>]	dical><full-title>Global Journal of Science Frontier Research Chemistry</full-title></periodical><pages>5, https://journalofscience.org/index.php/GJSFR/article/view/816/681</pages><volume>13(B)</volume><number>4</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]
Poloxamer 188 CASRN 691397-13-4	CAS Name: Oxirane, 2-methyl-, polymer with oxirane, triblock	polyoxypropylene (27) unit	two polyoxyethylene (80) units	~42-44 mN/m at ~0.5 wt% and 36°C [ADDIN EN.CITE ADDIN EN.CITE.DATA]	4.8×10^{-4} M or 0.4 wt% at 37°C [ADDIN EN.CITE ADDIN EN.CITE.DATA]
N,N-Dimethyl-dodecylamine-N-oxide*** CASRN 1643-20-5	Lauryl dimethylamine oxide CAS Name:1-Dodecanamine, N,N-dimethyl-, N-oxide	dodecyl group	amine oxide unit	34.1 mN/M at 1 g/L (0.1 wt.%) and 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14772</RecNum><Display	1.7×10^{-3} M or 0.039 wt% [ADDIN EN.CITE <EndNote><Cite><Author>Hoffmann</Author><Year>1990</Year><RecNum>14764</RecNu

				Text>[39]</DisplayText><record><rec-number>14772</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596028055">14772</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Dodecyldimethylamine oxide, CASRN: 1643-20-5, EC number: 216-700-6, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals	m><DisplayText>[40]</DisplayText><record><rec-number>14764</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026736">14764</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hoffmann, H.</author></authors></contributors><titles><title>Correlation between surface and interfacial tensions with micellar structures and properties of surfactant solutions</title><secondary-title>Progress in

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Anionic Surfactants					
Chemical Name in Text	**Other Relevant Names**	**Criteria 1**		**Criteria 2**	**Criteria 3**
		Hydrophobic group(s)	**Hydrophilic group(s)**	**Surface Tension**	**Critical Micel Concentration (CMC)**

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Sodium dodecyl sulfate CASRN: 151-21-3	SDS CAS Name: Sulfuric acid monododecyl ester sodium salt (1:1)	dodecyl group	sulfate group	35 mN/m at 0.29% (wt%) and 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Hernainz</Author><Year>2002</Year><RecNum>14768</RecNum><DisplayText>[42]</DisplayText><record><rec-number>14768</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027363">14768</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hernainz, F.</author><author>Caro, A.</author></authors></contributors><titles><title>Variation of surface tension in aqueous solutions of sodium dodecyl	8.25×10^{-3} M or 0.24 wt% at 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596026897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Crit

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				sulfate in the flotation batch</title><secondary-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</secondary-title></titles><periodical><full-title>Colloids and Surfaces A: Physicochemical and Engineering Aspects</full-title></periodical><pages>19-24, https://www.sciencedirect.com/science/article/abs/pii/S0927775701005751</pages><volume>196</volume><number>1</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>]	ical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dat

					es><year>1971</year></dates><urls></urls></record></Cite></EndNote>]
Oleoyl sarcosine CASRN 110-25-8	CAS Name: Glycine, N-methyl-N-((9Z)-1-oxo-9-octadecen-1-y	oleyl group	carboxylic acid anion	31.91 mN/M at (0.1% wt%) at 19.9°C** [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14767</RecNum><DisplayText>[43]</DisplayText><record><rec-number>14767</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027202">14767</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sodium N-methyl-N-(1-	2.6×10^{-3} wt% temperature not reported, assumed to be room temperature ~25°C [ADDIN EN.CITE <EndNote><Cite><Author>ChattemChemicals</Author><Year>2020</Year><RecNum>14769</RecNum><DisplayText>[44]</DisplayText><record><rec-number>14769</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027596">14769</key></foreign-keys><ref-type name="Journal Article">17</ref-

Commented [HT21]: Is this really right? Is this really M OR Is it 0.0026 wt%

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				oxo-9-octadecenyl)aminoacetate, CASRN 3624-77-9, EC number: 222-829-9, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://www.echa.europa.eu/fi/web/guest/registration-dossier/-/registered-dossier/5350/4/11</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>] **Note this reference is to the sodium salt.	type><contributors><authors><author>ChattemChemicals</author></authors></contributors><titles><title>Oleoyl Sarcosine, CASRN 110-25-8</title><secondary-title>Product Information</secondary-title></titles><periodical><full-title>Product Information</full-title></periodical><pages>https://www.chattemchemicals.com/</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>] **Note this reference is to the sodium salt.
Sodium lauroyl sarcosinate CASRN: 137-16-6	CAS Name: Glycine, N-methyl-N-(1-oxododecyl)-, sodium salt (1:1)	lauryl group	carboxylic acid anion	40.5 mN/m at 2% w/w ([redacted] wt%) and 20°C [ADDIN EN.CITE <EndNote><Cite><A	8.0×10^{-2} wt% Reference? Wayne's

Commented [HT23]: Really wt% or M
If wt% for consistency change to 0.08 wt%

Commented [HT22]: Assume w/w was as reported...what would be wt%?

				uthor>Dossier</Author><Year>2020</Year><RecNum>14770</RecNum><DisplayText>[45]</DisplayText><record><rec-number>14770</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027817">14770</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sodium N-lauroylsarcosinate, CASRN 137-16-6, EC number: 205-281-5, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-	

				title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/registration-dossier/-/registered-dossier/14123/4/11</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]	
Dioctyl Sulfosuccinate Sodium Salt CASRN: 577-11-7	DOSS Dioctyl sodium sulfosuccinate CAS Name: Butanedioic acid, 2-sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt	two 2-ethyl hexyl groups	sulfosuccinate group	<28 mN/m at 0.5 vol% and 25°C* [ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>1957</Year><RecNum>14755</RecNum><DisplayText>[46]</DisplayText><record><rec-number>14755</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596024	6.8×10^{-4} M or 0 wt% at 25°C [ADDIN EN.CIT <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0e

Commented [HT25]: g/L??

Commented [HT24]: Assume vol% is what reported...what would be wt%?

				180">14755</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, E.F.</author><author>Woodberry, N.T.</author><author>Dixon, J.K.</author></authors></contributors><titles><title>Purification and surface tension properties of alkyl sodium sulfosuccinates</title><secondary-title>Journal of Colloid Science</secondary-title></titles><periodical><full-title>Journal of Colloid Science</full-title></periodical><pages>452-459</pages><volume>12</volume><number>5</number><dates><year>1957</year	rr5sr" timestamp="15960 26897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Critical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared

				></dates><urls></urls></record></Cite></EndNote>]	under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dates><year>1971</year></dates><urls></urls></record></Cite></EndNote>]
Cationic Surfactants					
Chemical Name in Text	**Other Relevant Names**	**Criteria 1**		**Criteria 2**	**Criteria 3**
		Hydrophobic group(s)	**Hydrophilic group(s)**	**Surface Tension**	**Critical Micelle Concentration (CMC)**
Benzalkonium chloride CASRN: 8001-54-5	CAS Name: Quaternary ammonium compounds, alkylbenzyldimethyl, chlorides	alkyl chains are C12, C14, C16 and C18 and benzyl group	quaternary nitrogen	37 mN/m at concentrations greater than about 4×10^{-4}M and 25°C* [ADDIN EN.CITE <EndNote><Cite><A	C12: reported values range from 2.3 - 8.5×10^{-3} M or 0.078 - 0.29 wt% at 25°C

Commented [HT26]: Temp is provided only for some...is this acritical issue? Not part of the criteria...include of not?

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				uthor>Nandni</Author><Year>2013</Year><RecNum>14766</RecNum><DisplayText>[47]</DisplayText><record><rec-number>14766</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027033">14766</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nandni, D.</author><author>Mahajan, R.K.</author></authors></contributors><titles><title>Micellar and Interfacial Behavior of Cationic Benzalkonium Chloride and Nonionic Polyoxyethylene Alkyl Ether Based	C14: 3.7×10^{-4} M or 0.014 wt% C16: 4.2×10^{-5} M or 0.0016 wt% at 23°C C18: reported values range from 7.1 - 8.5×10^{-6} M or 0.0003 - 0.00036 wt% at 23°C [ADDIN EN.CITE <EndNote><Cite><Author>Mukerjee</Author><Year>1971</Year><RecNum>14765</RecNum><DisplayText>[41]</DisplayText><record><rec-number>14765</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="15960

Commented [HT29]: also at 23 C?

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				Mixed Surfactant Systems</title><secondary-title>Journal of Surfactants and Detergents</secondary-title></titles><periodical><full-title>Journal of Surfactants and Detergents</full-title></periodical><pages>587-599, https://doi.org/10.1007/s11743-012-1427-z</pages><volume>16</volume><number>4</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>]	26897">14765</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mukerjee, P.</author><author>Mysels, K.J.</author></authors></contributors><titles><title>Critical micelle concentrations of aqueous surfactant systems</title><secondary-title>Prepared under contract for the Office of Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</secondary-title></titles><periodical><full-title>Prepared under contract for the Office of

					Standard Reference Data, National Bureau of Standards of NSRDS-NBS 36, Washington, DC 20234</full-title></periodical><pages>242, https://nvlpubs.nist.gov/nistpubs/Legacy/NSRDS/nbsnsrds36.pdf</pages><dates><year>1971</year></dates><urls></urls></record></Cite></EndNote>]
Didecyldimethyl ammonium chloride CASRN 7173-51-5	DDAC CAS Name: 1-Decanaminium, N-decyl-N,N-dimethyl-, chloride (1:1)	decyl groups	quaternary nitrogen	25.82 mN/m at 1 g/L (0.1 wt%) and 20°C [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14771</RecNum><DisplayText>[48]</DisplayText><record><rec-number>14771</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5s	0.39 g/L or 0.039 wt% at 25°C [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14771</RecNum><DisplayText>[48]</DisplayText><record><rec-number>14771</rec-number><foreign-keys><key app="EN" db-

				r" timestamp="1596027946">14771</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Didecyldimethylammonium chloride, CASRN: 7173-51-5, EC number: 230-525-2, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/registration-dossier/-/registered-dossier/5864/4/11</pages><dates><year>2020</year></dates>	id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596027946">14771</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Didecyldimethylammonium chloride, CASRN: 7173-51-5, EC number: 230-525-2, Surface Tension</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.

				<urls></urls></record></Cite></EndNote>]	europa.eu/registration-dossier/-/registered-dossier/5864/4/11</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]

*Not all of the surface tension measurement references identified are run at exactly 20°C, but they are sufficiently close (within 5°C) so as not to affect the measurement. In addition, several measurements were run at 0.1% instead of the recommended 0.5%. Increasing the concentration to 0.5% is likely to lower the surface tension.

Commented [HT30]: Any reference for this?

**Carboxylic acid compounds, such as oleoyl sarcosine, have a carboxyl group pKa value of ~5, thus at physiological pH values maintained near 7 in the lung, the carboxyl group will be 99% in the anionic form according the Henderson-Hasselbalch equation. Since sodium is the major cation in mammalian body fluids (~145 mM), the use of the sodium oleoyl sarcosine surface tension value is appropriate for its characterization.

***Zwitterionic: At pH 7, 90% expected to be nonionic; only small amount cationic.

Hazard Identification

There is concern for dysfunction of natural surfactant in the lung from inhalation of surfactants. Additionally, there is evidence that some surfactants or similar structures may also interfere with the cell membrane [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The capacity of exogenous surfactants to interfere with pulmonary surfactant and impair pulmonary function has been demonstrated in human volunteers and in laboratory animals. The pulmonary response to surfactant aerosol is likely in proportion to the exposure concentration and duration, but available data on acute and repeated-dose effect levels are limited within each subcategory, which limits establishing a correlation between chemical properties and exposure methods (*e.g.,* aerosol droplet size) and toxicity.

Nonionic Surfactants

In Vivo Studies

Several studies were identified for the nonionic siliconized superinone respiratory detergent, formaldehyde, polymer with oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol (CASRN 25301-02-4; also known as Defomarie, Alevaire, Tyloxapol). Healthy human volunteers showed significantly decreased pulmonary compliance following acute inhalation of Defomaire beyond that produced by the distilled water control [ADDIN EN.CITE <EndNote><Cite><Author>Obenour</Author><Year>1963</Year><RecNum>13656</RecNum><DisplayText>[51]</DisplayText><record><rec-number>13656</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1479320595">13656</key></foreign-keys><ref-type name="Journal

Article">17</ref-type><contributors><authors><author>Obenour, R. A.</author><author>Saltzman, H. A.</author><author>Sieker, H. O.</author><author>Green, J. L.</author></authors></contributors><titles><title>Effects of surface-active aerosols and pulmonary congestion on lung compliance and resistance</title><secondary-title>Circulation</secondary-title><alt-title>Circulation</alt-title></titles><periodical><full-title>Circulation</full-title><abbr-1>Circulation</abbr-1></periodical><alt-periodical><full-title>Circulation</full-title><abbr-1>Circulation</abbr-1></alt-periodical><pages>888-92</pages><volume>28</volume><edition>OBENOUR, R A
SALTZMAN, H A
SIEKER, H O
GREEN, J L
1963/11/01</edition><keywords><keyword>Aerosols</keyword><keyword>Alcohols</keyword><keyword>Ethanol</keyword><keyword>Heart Failure</keyword><keyword>Humans</keyword><keyword>Infusions, Parenteral</keyword><keyword>Injections, Intravenous</keyword><keyword>Lung</keyword><keyword>Lung Compliance</keyword><keyword>Pulmonary Edema</keyword><keyword>Respiratory Function Tests</keyword><keyword>Silicones</keyword><keyword>Sodium Chloride</keyword><keyword>Surface-Active Agents</keyword></keywords><dates><year>1963</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>0009-7322 (Print)
0009-7322 (Linking)</isbn><accession-num>14079193</accession-num><call-num>0 (Aerosols)
0 (Alcohols)
0 (Silicones)
0 (Surface-Active Agents)
3K9958V90M (Ethanol)
451W47IQ8X (Sodium Chloride)</call-num><urls></urls><remote-database-provider>NLM</remote-database-

provider><language>Eng</language></record></Cite></EndNote>]. Increased minimum surface tension due to detergent was demonstrated, and shown to be dose-dependent, using pulmonary surfactant extracted from dogs and mixed *in vitro* with the nonionic surfactant tyloxapol (Alevaire) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. *In vivo* exposure of dogs to Alevaire in this study (8 h aerosol exposure; vehicle and concentration not reported) produced little effect (only 1/10 dogs exposed to Alevaire showed increased minimum surface tension), which the authors concluded support the dose-dependence of the effect and indicate that small amounts of detergent can be present in the lungs without detectably altering surfactant function [ADDIN EN.CITE ADDIN EN.CITE.DATA].

Other pulmonary effects in dogs and/or sheep exposed to nonionic surfactant, tyloxapol, included reduced oxygen content of arterial blood (*i.e.*, impaired gas exchange in the lung), increases in pulmonary extravascular water volume and wet-to-dry weight ratio of the lungs, and grossly visible pulmonary edema and atelectasis (*i.e.*, collapsed alveoli) [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In the study by Modell *et al.* (1969) [ADDIN EN.CITE ADDIN EN.CITE.DATA], no gross pathology differences were seen in detergent-exposed vs. control lungs of dogs, although some portions of both control and exposed lungs were heavy and discolored reddish-purple, which may have been caused by fluid accumulation from the liquid aerosol exposures and/or the use of hypotonic saline in the study (0.45% NaCl). Normal appearances were observed in the remaining areas of the lungs.

In rodent models, irritation and inflammatory effects on the respiratory tract has been observed with varying degrees of severity. Acute inhalation exposure to Polysorbate 20, which is not

irritating to the skin or eyes [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14776</RecNum><DisplayText>[52]</DisplayText><record><rec-number>14776</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596030693">14776</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sorbitan monolaurate, ethoxylated, 1 - 6.5 moles ethoxylated, CASRN: 9005-64-5, EC number: 500-018-3, Skin irritation/corrosion</title><secondary-title>European Chemicals Agency</secondary-title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/13525/7/4/2</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>], via nose-only administration for 4 hours in Wistar Han rats to a concentration of 5.1 mg/L (5,100 mg/m^3, MMAD 2.2 µm, GSD 2µm) did not observed an increase in mortalities, clinical signs, or abnormalities in the gross pathology [ADDIN EN.CITE <EndNote><Cite><Author>Dossier</Author><Year>2020</Year><RecNum>14777</RecNum><DisplayText>[53]</DisplayText><record><rec-number>14777</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596030813">14777</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Registration Dossier</author></authors></contributors><titles><title>Sorbitan monolaurate, ethoxylated 1 - 6.5 moles ethoxylated, CASRN: 9005-64-5, EC number: 500-018-3, Acute Toxicity: Inhalation</title><secondary-title>European Chemicals Agency</secondary-

title></titles><periodical><full-title>European Chemicals Agency</full-title></periodical><pages>https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/13525/7/3/3</pages><dates><year>2020</year></dates><urls></urls></record></Cite></EndNote>]. The total lung deposition mass was calculated to be 6.6×10^4µg using MPPD modeling. A respiratory irritation study on a mixture containing octylphenoxypolyethoxyethanol [ADDIN EN.CITE ADDIN EN.CITE.DATA], which can be severely irritating to the skin and eyes in male Webster mice using the ASTM Method E981 where animals were exposed for 3 hours to concentrations of 12, 22, 51, 118, and 134 mg/m^3 and allowed 30-60 minutes recovery time observed signs of respiratory irritation in animals at the three highest concentrations as indicated by increased respiratory frequency without an increase in pulmonary edema or lung weight [ADDIN EN.CITE <EndNote><Cite><Author>Alarie</Author><Year>1992</Year><RecNum>14778</RecNum><DisplayText>[54]</DisplayText><record><rec-number>14778</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1596035219">14778</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alarie, Y.</author><author>Stock, M.F.</author></authors></contributors><titles><title>Respiratory Irritancy on a Mixture containing Polyethylene Glycol Mono(Octyl)Phenyl Eether CAS #9035-19-5</title><secondary-title>ChemView - U.S. Environmental Protection Agency</secondary-title></titles><periodical><full-title>ChemView - U.S. Environmental Protection Agency</full-title></periodical><pages>37, https://chemview.epa.gov/chemview/proxy?filename=09022526800b76c9_86960000465_09-26-2011_8D_PHCS_Original%20-

%2086960000465.pdf</pages><dates><year>1992</year></dates><urls></urls></record></Cite></EndNote>]. An acute inhalation exposure study in Syrian hamsters to 3.0 mg/L of octylphenoxypolyethoxyethanol to varying exposure durations reported that lung deposition of octylphenoxypolyethoxyethanol corresponded to mortality with an LD_{50} of 1300-2100 µg [ADDIN EN.CITE <EndNote><Cite><Author>Damon</Author><Year>1982</Year><RecNum>13323</RecNum><DisplayText>[55]</DisplayText><record><rec-number>13323</rec-number><foreign-keys><key app="EN" db-id="sp9w2fxejsw0zre0azr5evearxfds0err5sr" timestamp="1479320592">13323</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Damon, E. G.</author><author>Halliwell, W. H.</author><author>Henderson, T. R.</author><author>Mokler, B. V.</author><author>Jones, R. K.</author></authors></contributors><titles><title>Acute toxicity of polyethylene glycol p-isooctylphenol ether in syrian hamsters exposed by inhalation or bronchopulmonary lavage</title><secondary-title>Toxicology and applied pharmacology</secondary-title><alt-title>Toxicol Appl Pharmacol</alt-title></titles><periodical><full-title>Toxicology and Applied Pharmacology</full-title><abbr-1>Toxicol. Appl. Pharmacol.</abbr-1></periodical><pages>53-61</pages><volume>63</volume><number>1</number><edition>Damon, E G
Halliwell, W H
Henderson, T R
Mokler, B V
Jones, R K
1982/03/30</edition><keywords><keyword>Animals</keyword><keyword>Cricetinae</keyword><keyword>Detergents/ toxicity</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Female</keyword><keyword>Lethal Dose 50</keyword><keyword>Lung/ drug

effects/pathology</keyword><keyword>Male</keyword><keyword>Mesocricetus</keyword><keyword>Octoxynol</keyword><keyword>Polyethylene Glycols/administration & dosage/toxicity</keyword><keyword>Surface-Active Agents/toxicity</keyword><keyword>Therapeutic Irrigation</keyword></keywords><dates><year>1982</year><pub-dates><date>Mar 30</date></pub-dates></dates><isbn>0041-008X (Print)
0041-008X (Linking)</isbn><accession-num>7071873</accession-num><call-num>0 (Detergents)
0 (Surface-Active Agents)
30IQX730WE (Polyethylene Glycols)
9002-93-1 (Octoxynol)</call-num><urls></urls><remote-database-provider>NLM</remote-database-provider><language>Eng</language></record></Cite></EndNote>]. The authors concluded that the deaths in these animals were likely the result of severe laryngeal edema and ulcerative laryngitis while the lower airways and lungs in these animals were relatively free of serious pathologies. The authors hypothesized that that these observed effects were due to large tracheobronchial deposition following the aerosol exposure and the mucociliary clearance of the deposited chemical resulted in a large concentration of the chemical on the laryngeal mucosa. Finally, in the only repeated dose inhalation exposure identified for nonionic surfactants, a 2-week repeated whole-body dose inhalation study was conducted on octylphenoxypolyethoxyethanol in male and female Sprague-Dawley rats to 5.3 and 10.3 mg/m^3 (5/sex/dose; MMAD 1.8 µm, GSD 1.8µm) for 6 hours/day, 5 days/week [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Slight to minimal subacute inflammation of the alveolar walls and hyperplasia of the alveolar/bronchiolar epithelium was reported, in addition to an increase in slight discoloration of the lungs, increased lung weight, and mucoid nasal discharge; a LOAEC of 5.3 mg/m^3 was identified.